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INFECTIOUS DISEASES

THEIR ETIOLOGY, DIAGNOSIS, AND TREATMENT

BY

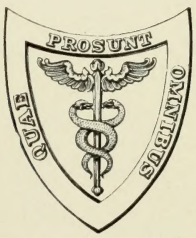
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ILLUSTRATED WITH FORTY-THREE ENGRAVINGS



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PREFACE.

THOSE members of the profession who confine their reading to English alone will welcome this translation of Professor Roger's great work. His subject comprehends almost the entire scope of internal medicine and touches many of the principles underlying modern surgery as well.

During the last decades the marvellous discoveries in pathology have succeeded one another with such bewildering rapidity that time has apparently been lacking for the assimilation of the newly acquired knowledge; and, as a result, many have failed to correlate the new theories with the old facts. The effect of the present volume is to harmonize any seeming antagonism between experimental research and clinical observation, and to reduce the theories of infection and immunity to the basis of practical utility.

This material could not have been prepared by a laboratory investigator however brilliant, nor by a clinician however profound his experience, nor yet could it have been the product of collaboration; its creation remained for one who combined the instincts and training of a student at home in original research with almost unprecedented opportunities for clinical investigation. Possessed of an equal facility in each, Professor Roger has pursued clinical and experimental researches jointly, although he always subordinates the latter to the former and never loses sight of the fact that the purpose of the laboratory is to amplify and explain clinical observations, to the end that from both the therapist should receive information indispensable to practical results.

With the directness of the true philosopher, the author unfolds his subjects by using the simplest methods. He first studies the

pathogenic agents, inquires into their distribution in nature, the conditions under which they attack man, and their mode of invasion. Full consideration is then given to their influence upon the human economy and the reaction of the latter upon the invaders. Heredity, predisposition, and immunity receive specific and general attention, while to the more directly practical departments of diagnosis, prognosis, and treatment, both preventive and curative, ample time and space are devoted.

While the reading of no page may be omitted without loss, it is desired to direct special attention to the author's consideration of the influence of infection upon the various organs of the body —his researches in experimental appendicitis, pseudotuberculosis, variola, and the vesicatory test; also to his admirable treatment of the pathology of fevers and the defenses of the organism against infections. The final chapters, comprising more than a quarter of the volume, are devoted to a masterly discussion of the therapeutics of infectious diseases.

As a basis for his opinions in the matter of treatment, as well as the clinical observations reflected throughout the work, Professor Roger has had recourse to the opportunities afforded him at the Hôtel Dieu and the isolation wards in the hospital of Porte d'Aubervilliers. In these, the latter of which receives all cases of contagious diseases occurring in Paris, he personally attended over ten thousand patients during a period of five years.

The author knows his subject thoroughly, and, like a strong man rejoicing in his strength, he takes a keen delight in grappling with its problems. No doubt many readers will join him in this pleasure and thereby become stronger men.

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CONTENTS.

PAGE

CHAPTER I.

General Considerations 17

CHAPTER II.

General Characters of Pathogenic Bacteria 43

CHAPTER III.

Etiology of Infections 64

CHAPTER IV.

Pathogenesis of Infections 98

CHAPTER V.

Microbic Associations 135

CHAPTER VI.

Defenses and Reactions of the Organism 154

CHAPTER VII.

Suppuration 182

CHAPTER VIII.

Gangrene 225

CHAPTER IX.

Septicemias and Pyemias 244

CHAPTER X.

Nodular Infections 272

CHAPTER XI

Cellular Degenerations 323

CHAPTER XII.

PAGE

General Reactions—Fever 333

CHAPTER XIII.

Influence of Infections upon Various Parts of the Organism . 359

CHAPTER XIV.

Influence of Infection upon the Various Parts of the Organism (*Continued*) 402

CHAPTER XV.

Influence of Infection upon the Various Parts of the Organism (*Continued*) 442

CHAPTER XVI.

Influence of Infections upon the Various Parts of the Organism (*Concluded*) 469

CHAPTER XVII.

Evolution of Infectious Diseases 494

CHAPTER XVIII.

The Consequences of Infection 541

CHAPTER XIX.

Mechanism of Immunity and of Predisposition . . . 551

CHAPTER XX.

Congenital Infections and Heredity 580

CHAPTER XXI.

Diagnosis and Prognosis of Infectious Diseases . . 606

CHAPTER XXII.

Therapeutics of Infectious Diseases 642

CHAPTER XXIII.

Therapeutics of Infectious Diseases (*Concluded*) 757

CHAPTER XXIV.

Hygiene and Prophylaxis of Infectious Diseases . . . 837

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INFECTIOUS DISEASES.

CHAPTER I.

GENERAL CONSIDERATIONS.

Definition of Infectious Diseases. The Artificial Limits of this Group. Transition between Infectious and Parasitic Diseases. Classification of Infectious Diseases. Historical. Ancient Views of Infections. Analogy between Infections and Fermentations. Researches upon the Animate Agents of Infections. The Pathogenic Bacteria. Pathogenic Plants and Animals. Classification of Infectious Agents.

Definition. The term "infection" is one of those words which are most frequently employed in medicine and of which the meaning has been most notably modified by time. While it was well defined by the ancients, it is employed by modern authors without any attempt to designate the precise meaning attributed to it at the present day.

To the ancients "infection" meant everything that contaminates the air.[1] From the time of Lucretius, Ovid, and Virgil until the days of Copland, the word was employed in this sense. The same idea was expressed by Dupuytren, who believed that the cause of infection resided in the action exerted upon the air by people crowded into low, narrow, dark, and dirty localities, and by decaying vegetable or animal substances. The air, when contaminated by such emanations, becomes a true toxic agent.

It was only at a recent date that an attempt was made to differentiate infection from contagion.[2] The two definitions proposed by De la Berge, Monneret, and Fleury in their compendium[3] give a clear idea of the conceptions prevailing in the first half of the nineteenth century.

[1] Infection, from Latin *infectionem, infectus,* infect, or more exactly, impregnated; *in, facere,* to make in, to put in.

[2] Contagion, *contagio,* from *cum, tangere,* to touch. This term is applied to diseases which originate by contact.

[3] Compendium de méd. pratique, 1837, vol. ii. p. 463; vol. v. p. 167, 1842.

"Infection," they say, "is the mode of propagation of certain diseases which depend upon the toxic or morbific action exerted by decaying vegetable or animal substances and the miasms exhaled by the healthy or diseased human body upon one or several individuals placed under conditions which render them particularly susceptible to their influence.

"Contagion is that mode of propagation of disease by which an afflicted individual communicates the malady to others favorably situated to receive it, and the latter, in their turn, become agents of propagation of the disease the characters of which remain identical throughout."

It is interesting to note that in the foregoing two definitions the authors admit the necessity of morbid opportunity for the genesis of infectious and contagious diseases—a conception that has been fully confirmed by recent researches. On the other hand, the contagious diseases which are always reproduced with the same characters belong to what are at present designated as infectious diseases. It is to be noted, however, that in passing from one individual to another, the disease does not always preserve its primitive character. Erysipelas, for instance, may engender puerperal fever. The definition of infections is still less successful, for it is applicable to a great variety of morbid states due to intoxications. This confusion is encountered even in recent works. Several processes that are in reality to be attributed to autointoxication have been described under the name of autoinfection.

It is thus evident that, toward the middle of the nineteenth century, the diseases transmitted through the agency of air—*i. e.*, miasmatic diseases—were considered as infectious and were clearly distinguished from those conveyed by contact, either mediate or immediate.[1] The limits of infections, however, were soon to be widened. The miasmatic diseases were classed with those arising from inoculation or absorption of decaying organic substances. The group of autoinfections were thus created and included the two great processes which are still designated as purulent and putrid infection.

We are thus brought to the present time, when investigators seeking for the causes of these miasmatic diseases, putrid and purulent, demonstrated the intervention of microscopic animate agents. These animate agents were first discovered in the air, and the miasmatic

[1] Chomel. Eléments de path. générale, Paris, 1863, 5th ed., p. 38.

theory thus received experimental sanction. Next, they were frequently seen to vegetate upon our integuments and mucous membranes, and the theory of autoinfection was established upon an unassailable basis.

From that time infectious diseases were naturally considered to be always dependent upon some animate agent. They constitute a particular, autonomous group in the class of parasitic diseases.

Agreement upon this point is unanimous. Difficulty arises, however, when an attempt is made to learn the distinctive characters separating infection from parasitism. The clinical symptoms, of course, are not comparable. No one would consider as infectious the manifestations caused by tænia or the slight dermatitis excited by *microsporon furfur*. Nevertheless, considerable embarrassment is experienced when accurate definitions are to be formulated. Hence, most authors have avoided offering any, depending upon the ability of the reader to comprehend what they were incapable of defining.

In view of these difficulties, some authors sought the characteristics of infection in the agents generating the morbid manifestations, and proposed to reserve the name infectious for diseases depending upon the action of bacteria. To the author this view does not seem acceptable. It is impossible to make etiological and pathogenic conceptions the exclusive basis of a classification. The nosographer must, first of all, weigh the various reactions of the organism, viz., the symptoms presented by the patient; he must start from the disturbances observed during life and proceed from the apparent phenomena to the hidden cause.

The ancient physicians succeeded in individualizing typhoid fever, anthrax, glanders, leprosy, and tuberculosis by the attentive study of symptoms. Pathological anatomy completed the work begun by clinicians. Modern researches in etiology have added little to ancient conceptions and, in the majority of instances, have confirmed them. Laennec's genius established the unity of tuberculosis merely through the data furnished by clinical observation and macroscopic anatomy. The histological researches of Grancher and Thaon confirmed Laennec's conception. Koch's discovery, completing Villemin's work, furnished an unassailable basis for ancient ideas. It did no more than permit the recognition of the tubercular character of some less clearly defined lesions of minor importance.

Clinical observation did not require the assistance of bacteriology in describing the eruptive fevers. Nothing is better established than

this part of medicine. Mediate or immediate contagion, regular or irregular types, malignant or benign, early or belated complications, all had been observed by the older physicians, and it is hardly probable that the discovery of the agents giving rise to these infections will greatly modify the ancient descriptions.

Should bacteriological research be taken as an exclusive basis it would lead to the separation of certain diseases which clinical observation seems to have rightly classed together. Paludism is the most characteristic type of miasmatic infections. It is produced, not by bacteria, but by animal parasites—protozoa. Accordingly, it should be excluded from the group of infections, a step which no observer would approve. The same is true also of smallpox, varicella, and vaccinia, provided, as numerous investigations tend to prove, we admit that they are due to animal parasites. Nevertheless, by their symptomatic and contagious characters, they head the list of infectious diseases.

The study of tuberculosis and actinomycosis furnishes fresh confirmation for our view. Clinical observers had noted strong analogies between these two diseases. Bacteriology widened the breach separating them. One of them, tuberculosis, was classed among the infections, since it depends upon a bacillus; the other, actinomycosis, was included with parasitic diseases, as it is due to an algæ whose organization is far more complex. Recent researches, however, tend to justify the clinical view by establishing a close relationship, at first unsuspected, between the two pathogenic agents. The infective agent of tuberculosis seems to have unduly occupied a place among the bacilli. Under certain conditions this plant presents prolongations, ramifications, and swellings: it assumes the aspect of actinomyces, and, like it, enters into the group of *streptothrix* or *oöspora*. Additional inquiry has thus established an etiological analogy corresponding to symptomatic analogy. If, however, bacterial diseases alone should be considered as infectious, tuberculosis would have to be excluded from the group of infections. If, on the other hand, tuberculosis should be retained in that group, then actinomycosis should also be assigned a like position; and there remains no reason why those diseases which are caused by a certain species of *aspergillus* or certain yeasts should not be placed in the same category.

Abandoning etiological classification, some authors have chosen pathogenesis as a basis. A disease should be called infectious or parasitic, according to the mode of action of the cause. In the former

case the morbific agent acts by the soluble substances which it secretes; in the latter instance its action is merely a mechanical one —some form of traumatism inflicted upon the tissues.

Such a conception is better. It would be perfect if we knew with greater accuracy the mode of action of the pathogenic agents. At any rate, this pathogenic classification does not differ greatly from symptomatic classifications, which I prefer. If the reactions presented by diseased organisms are of the same nature, the reason is that the mode of action of the agents calling them into play are analogous. Classifications based upon pathogenesis are, however, hardly possible as yet. Too much obscurity and discord still prevail in this branch of medicine. It is, therefore, better to rely upon the symptoms presented by the sick. This method is simpler and, it seems to the writer, even more rational. For the philosopher as well as for the practitioner, a classification must be founded upon observable and not upon hidden signs. We observe the morbid disturbances, the clinical manifestations, and their study enables us to discover the lesions which accompany them, the causes which produce them, and the mechanism which accounts for them.

What, then, are the clinical characters which will enable us to recognize the infectious nature of a disease?

In many instances it is possible to ascertain the contagious nature and epidemic progress of a disease; but this is not sufficient to prove its infectious character. Certain nervous affections are contagious and epidemic. The history of insanity and hysteria furnishes numerous illustrations of this. The distinction is, as a rule, easy, though not always. It was long believed that the contagiousness of whooping-cough was due to nervous influence—some sort of imitation. To-day it is known that there is actual transmission of a living germ. The difficulty is as great with regard to intoxications. Poisoning is at times epidemic or endemic, the affected individuals having absorbed nearly equal amounts of noxious substances. In infections, particularly in those of aquatic origin, the study of etiological conditions shows that the pathogenic agent was imponderable, and that it must have increased by reproduction within the organism, which fact demonstrates its animate nature. The surgical or puerperal septicemias transmitted through insufficiently cleansed instruments or hands are of this nature.

In order that animate agents may develop and give rise to disturbances, a certain length of time must elapse between their intro-

duction into the system and the appearance of the first morbid reactions. This is the period of incubation. It properly belongs to infectious and parasitic diseases. In practice, however, it is often impossible to distinguish the incubation period from the period of latency observed under a great number of circumstances, notably in intoxications and, at times, also in nervous reactions.

When the microbe is sufficiently developed the organism reacts by two orders of manifestations, namely, local and general. The local reactions cannot serve to characterize infection, for they appear in many parasitic diseases, and also in various intoxications. The general reactions, including fever, are likewise observed in poisonings, in autointoxications—gout, for example.

Thus, taken separately, each of the characters of infection presents nothing special. We must, therefore, acknowledge the singular genius of the early observers who, in the midst of analogous etiological conditions and comparable symptomatic manifestations, were able to classify the infectious processes. Modern researches have in almost every instance confirmed the results of their intuition, adding an element of certainty by the discovery of the animate agent.

In our definition of infectious diseases we must, therefore, emphasize the animate nature of the pathogenic agent. We will state that infectious diseases belong to the class of parasitic diseases; but they here occupy a special place. How can we distinguish them?

Despite our endeavors, the distinction will necessarily be an artificial one. All attempts at classification are arbitrary, since distinctions rest only upon differences of degree. However, let us attempt to point out the limits between the two groups.

The fundamental character of the parasite is to live at the expense of the being it inhabits without endangering the existence of its host. It exerts as little harmful influence upon the host as possible. If it ever causes death it is as a matter of accident. Parasites, such as intestinal worms and cutaneous parasites, do exert a toxic action, but this is of a local character. The blue spots caused by the *pediculis pubis* express an intoxication which does not extend beyond the integument. The pustules of scabies are produced by secondary infections facilitated by the presence of the specific agent. At all events, general reactions are absent, and if any do occur, they are of a reflex nature, such as might be occasioned by any foreign body, even of inorganic nature, that irritates the nerve terminations. Even

hydatid cyst is capable of exerting only mechanical action. If, at a given moment, it gives rise to serious symptoms, it is simply by virtue of its excessive development, under which circumstances it compresses the adjacent organs. At any rate, it does not act otherwise than would any other foreign body of the same size.

It is to be noted, however, that all parasites contain and produce toxic substances. It is a general law of biology that vital manifestations result in the formation and excretion of noxious products. On the other hand, a foreign body, whether of organic or inorganic nature, provokes no reaction, either local or general, except through the agency of the soluble substances which it diffuses. An absolutely insoluble body excites no reaction whatever. While the amount of dissolved matter is sufficient to influence the living cells and particularly the nerve endings, it is at times too small to be detected by our chemical reagents. Raulin's and Naegeli's experiments in this connection are altogether conclusive. These reflections show the insignificant value of our classifications and demonstrate that the various pathological processes are related to each other by insensible transitions.

It may further be objected that certain living beings may, under certain conditions, be considered parasites or infectious agents. Such, for instance, is the case with *oidium albicans*, which is a simple epiphyte in man and an infectious agent in animals. I think these fungi should be classed with the infectious agents and not with the true parasites, for they are capable of causing in animals a mycosis analogous to bacterial diseases. Moreover, their subcutaneous inoculation often gives rise to grave general manifestations, and may produce death in a few days. In man such an evolution is rare, but we also find similar facts among bacteria. The pneumococcus, streptococcus, staphylococcus, and colon bacillus live upon our mucous membranes as inoffensive parasites. They sometimes provoke small superficial lesions of no greater importance than a patch of aphtha. On other occasions they rise to the rank of infectious agents and cause violent reactions.

These few examples show how numerous are the transitions between infectious and parasitic diseases. Nevertheless, I believe it is possible to distinguish the two groups of animate agents in the following manner:

Parasitic agents exert a simple mechanical action upon the economy. The toxic substances produced by them are not sufficiently

powerful to appreciably impress the whole organism. They give rise only to some local phenomena.

The action of infectious agents upon the organism is complex. Their mechanical rôle is very little, if at all, marked. They act mainly through the noxious substances elaborated by them. For this reason it is possible to say that infection, in the last analysis, is intoxication of parasitic origin.

It will now be easier for us to understand how the group of infections should be formed. Inspired with the definition proposed by Prof. Bouchard for disease in general, we shall say: *Infectious diseases are characterized by the phenomena manifested in an individual when undergoing the action of parasitic toxins and reacting against them.*

Objections could be raised against this definition. It seems to the writer, however, that it is quite in harmony with facts actually known. It has the advantage of placing clinical phenomena in the first rank, and at the same time it takes cognizance of etiology and pathogenesis. If it is applicable to certain parasitic diseases, it is so for the reason that facts constitute an uninterrupted chain in nature.

Classification of Infectious Diseases.

An exclusively microbiological classification is impossible, since apparently identical clinical manifestations may be caused by different microbes, and, on the other hand, one and the same microbe may give rise to quite different manifestations.

These facts are well known. Suppuration, for instance, may be engendered by the most diverse bacteria. Likewise, in intoxications, many poisons produce the same symptoms: convulsions, paralyses, coma. To recall a simpler illustration, excitation of a nerve, whatever the irritant employed, whether physical, chemical, or physiological, always produces the same effect. The organism has at its disposition but a limited number of responsive modes; hence it is conceivable that, in pathology as well as in physiology, different excitations may be followed by similar reactions.

To return to the microbes. Bacteriological researches have demonstrated that ulcerative endocarditis may be the result of the action of the most varied microbes. The same is true in regard to bronchopneumonias, and the anatomicoclinical distinctions which some authors have attempted to establish according to the nature of the

pathogenic agent have been proved untenable by further researches. On the other hand, the same microbe is capable of exciting markedly dissimilar manifestations. The streptococcus, for instance, produces phlegmon, erysipelas, septicemias, pyemias, bronchopneumonias, ulcerative endocarditis, etc. The same is true of the staphylococcus, pneumococcus, and colon bacillus, which are met with in a great variety of lesions.

In view of these facts, some authors attempted to attack the modern theories of pathogenesis and to minimize the importance attributed to microbic agents. It must be acknowledged that at first the results seemed somewhat deceiving; but a comparative study of the events occurring in infections and in intoxications will show that the same difficulty exists in both.

Any given poison may exert wholly different effects. Alcohol, for instance, may cause drunkenness, delirium tremens, pachymeningitis, pseudotabes, hepatic cirrhosis, etc. The same is true of other poisons, such as phosphorus, arsenic, lead, and mercury. On the other hand, apparently identical phenomena may be due to the action of different poisons or occur even without the agency of any intoxication.

The results are, therefore, comparable in the various morbid groups, and their study clearly demonstrates the impossibility of purely etiological classifications. The inconstancy of results does not, however, constitute an exception to determinism, which is the basis of all science. If the manifestations are dissimilar while the cause is the same, this is due simply to the fact that the action of the cause is exercised under different conditions. We must remember that no two individuals are alike. Heredity and innateness impose upon each person a particularism which becomes more marked as years pass and the organism is subjected to numerous external influences. Since individuals are different, reactions cannot be identical. The facts observed by the physician are not, therefore, results of accident, but they are so complicated and so varied that it is impossible to unite them in a simple formula.

These reservations should not prevent the nosologist from taking cognizance of etiological data which, though always interesting, have acquired additional importance since the discovery of specific serums. Bacteriological subdivisions should, therefore, be introduced into clinical groupings.

Specific and Non-specific Infections. In the first place, infections may be divided into two large classes, specific and non-specific.

In specific infections the pathogenic agent suffices to characterize the disease. Such, for instance, are anthrax, tuberculosis, and diphtheria. This class is divisible into three orders according as the pathogenic parasite is a bacterium, a more highly organized plant, or an animal agent. A fourth order, which will sooner or later disappear, comprises those infections, such as hydrophobia, syphilis, typhus fever, and scarlatina, the pathogenic agents of which have not yet been discovered.

Non-specific infections differ from the preceding by the following characters: 1. They are due to common bacteria almost constantly inhabiting our mucous membranes and skin, vegetating as simple saprophytes. 2. Each clinical type may be produced by different agents. 3. Each microbe may give rise to the most varied manifestations.

Non-specific infections comprise exudative inflammations, such as erysipelas; suppurative processes, such as phlegmon; degenerative conditions, such as grave icterus; pseudomembranous inflammations, such as certain non-diphtheritic sore throats; ulcerating affections, such as infectious endocarditis, and necrosing processes, such as pulmonary gangrene. Now, the feature of dominant importance in the history of these diseases is not the nature of the pathogenic agent, but the morbid localization. The same microbe, staphylococcus aureus, for example, produces furuncle, osteomyelitis, and ulcerative endocarditis, yet no one would think of including in one chapter affections so different from each other. These non-specific infections must, therefore, be considered in connection with the organs in which the process is localized, and with other ulcerations which may affect the same viscera.

Subdivisions of Specific Infections. We will admit two groups in the class of specific infections, placing general infections of septicemic or pyemic character in the first group, and in the second those in which visceral localization immediately attracts the clinician's attention as a matter of prime importance.

The general specific infections comprise three classes: eruptive infections, septicemic infections, and infections with nodular productions.

Eruptive infections possess an indisputable autonomy. They cannot be ranked among infections with cutaneous determination. They are general diseases, veritable septicemias, ushered in with symptoms expressing an impregnation of the whole organism. Sub-

sequently a sort of discharge toward the mucous membranes and the skin takes place, relieving the principal symptoms. The discharge may be characterized by erythema, as in measles, scarlet fever, rubeola, and sudor anglicus; by vesicles, as in zona; by bullæ, as in varicella and polymorphous erythema; by vesicopustules, as in vaccinia and smallpox. Here belongs syphilis. "Venereal diseases" is a denomination which should become obsolete or be preserved only for convenience. Otherwise, it is wrong to form a group of diseases which have no relationship to each other except the fact that in the majority of cases they are contracted through sexual intercourse, though this etiological circumstance is not indispensable. Syphilis begins as a local lesion, followed by a general impregnation of the economy. Later on a discharge takes place toward the integuments. This evolution, although slower, is identical with that of smallpox. The comparison is altogether perfect if we select inoculated smallpox: in this case there is a local lesion followed by general impregnation and secondary eruption. The only difference resides in the fact that syphilis runs a much slower course and, therefore, the reactions are less intense. It is well, however, to remark that the comparison is exact only during the first periods of the disease. After a certain lapse of time syphilis gives rise to lesions which render it quite unlike eruptive fevers. At this stage, however, the virus is profoundly modified. Its contagiousness is *nil* or so slight that contamination by tertiary accidents was long denied, and very few cases are quoted even at the present day. This leads to the belief that syphilis is due to a parasite which undergoes a long course of evolution within the infected organism. After having provoked a highly contagious exanthematic septicemia, it becomes localized at certain points and produces local and non-transmissible lesions of a quite different nature.

The second group comprises the *infections with septicemic tendency* exclusive of eruptive fevers. The author classes in this group typhoid fever, typhus, influenza, bubonic plague, and anthrax. Typhoid fever might be placed among infections of an intestinal determination, but the digestive disturbances, important as they are, do not represent the principal symptom of the malady. The general reactions expressing the impregnation of the whole organism are of greater importance. The same remark is applicable to bubonic plague, the danger from which likewise results from the invasion of the organism by the specific bacillus. The same is true of anthrax:

it is not the local lesion that kills; on the contrary, the prognosis depends upon the resistance of the organism to general infection.

The infections with nodular productions seem to me to constitute a group so natural as to require no further discussion. Glanders links this group with septicopyemic infections. Tuberculosis, leprosy, and nodular mycoses are characterized by entirely comparable reactionary manifestations.

Non-specific infections are classified according to the predominating symptoms. In the majority of cases these symptoms are explained by the localization of the parasite. Tetanus alone is to be excepted. The author has placed this disease among the infections with nervous localization. Of course, the pathogenic agent remains localized at some point of the economy, most frequently in the cellular tissue, at times in some organ, and does not reach the nerve centres at all, thus behaving otherwise than the parasite of hydrophobia. The nervous manifestations are, however, so predominant that the clinician hesitates to assign to tetanus some other position in nosology. At all events, the author's view is in accordance with his definition of infectious diseases, since their characteristics must be sought in the reaction of the organism to the action of microbic toxin. The localization of the latter should guide the nosologist.

The writer has advisedly closely allied recurrent fever and paludism. These two diseases seem to form a very natural group in the classification. Their agents localize themselves in the organs connected with the blood system, notably in the spleen, and, at a certain moment, invade the blood itself.

As to the other infections, classification was easier. It was quite natural to place dysentery and cholera among infections with intestinal determination; yellow fever among infections with hepatic determination, etc.

The author's classification is, of course, subject to modification. He has, however, taken into account the chief characters of infections without neglecting the etiological data. He subdivides all infections, according to the causative agent, into infections of bacterial, mycosic, or animal origin. In a last group are placed those diseases in which the causative agents are as yet unknown.

				Bacterial.	*Mycosic.*	*Animal.*	*Unknown.*
Infections							
Specific	general	eruptive	erythematous	measles (?).		zona (?).	rubeola.
			vesicular.			varicella.	scarlatina.
			bulbous.			vaccinia.	sudor anglicus.
			pustular.			variola.	polymorphous erythemas.
			polymorphous.				
		septicemic		typhoid.			
				plague.			syphilis.
				influenza.			
				anthrax.			typhus.
		with nodular productions		glanders.			
				tuberculosis	actinomycosis.		
				pseudotuberculoses	botryomycosis.		
				leprosy	aspergillosis.		
	localized in the	digestive apparatus		cholera	saccharomycoses.		
				dysentery.		amebic dysentery.	
		liver		yellow fever.			
		larynx.					whooping-cough.
		glandular organs		mumps.			
		skin and mucous membranes	with pseudomembranous tendency	diphtheria.			
			suppurating	gonorrhœa.			
			ulcerating	soft chancre.			
		cellular tissue		gaseous gangrene.			hydrophobia.
		nervous system		tetanus.			
				epidemic cerebrospinal meningitis.		paludism.	
		serous membranes		acute articular rheumatism (?)			
		hematopoietic organs		recurrent fever.			
Non-specific	general			septicemia.	exudative.		
				pyemia.	suppurative.		
					degenerative.		
	localized in	organs		inflammations	pseudomembranous.		
		tissues			ulcerative.		
		systems			gangrenous.		

This classification is naturally of a provisional character. Tuberculosis, for instance, has been placed in its customary position—viz., among bacterial infections. It should, however, be classed with mycosic infections if its agent is an *oöspora*. In view of the contributions of Lesage, Achalme, Triboulet, Coyon, Laveran, and Catrin, the author has, with reserve, classed measles, acute articular rheumatism, and mumps as bacterial infections. Supported by researches which the writer is pursuing with Dr. Weil, and by the more recent work of Funck, smallpox, varicella, and vaccinia have been placed among the diseases due to animal microbes. Finally, dysentery has been divided into two distinct affections which are akin symptomatically, but different as to their pathogenic agents.

Tumors and lymphadenia are excluded, although their parasitic nature seems highly probable.

In this tentative classification of infectious diseases the actual process alone is taken into account, viz., that which is connected with the life of the pathogenic agent. When the latter is destroyed the morbid evolution does not stop. Here is brought to light an interesting difference between parasitic and infectious diseases: in the former all symptoms vanish with the parasite; in the latter certain disturbances persist and run an independent course of evolution. Organic affections, which are often developed in a slow, insidious manner, are thus created, and in some accidental way a cardiac lesion, for instance, connected with a typhoid fever suffered in childhood, and which has taken fifteen or twenty years to develop, is discovered in the adult. This, however, is of little practical importance, since the organic lesion is wholly independent of the causative affection of long ago. The sequelæ of infections are, therefore, rightly described as affections of the organs bearing no stamp of their origin.

History of Infectious Diseases.

It has always been admitted that infectious diseases may be transmitted by the air and by contact with the sick. Hippocrates speaks solely of the former mode, as do also the writers and poets. As late as the sixteenth century no important document concerning the contagiousness of disease is furnished us by medical literature. The ancients were not, however, ignorant of the transmission of disease by contact. It was evidently for fear of contagion that Moses ordered the isolation of persons afflicted with leprosy or gonorrhea. It was

the same etiological notion that, at the end of the fourteenth century, caused in Italy the isolation of persons who had come in contact with plague-stricken individuals.

Disregarding the useless controversy which raged about the question of the contagiousness of diseases, let us briefly review the ideas which successively prevailed as to the nature of the principles that served for their transmission.

Two great theories have always been advocated. One, the chemical, assumes the cause of diseases to be a volatile or fixed principle emanating from the soil, bodies of animals, or men. The other, a vital one, asserts the action of infinitely small living beings which penetrate and develop within the organisms of men or animals.

Some of the advocates of the chemical doctrine thought the morbific principles were volatile. This conception was so deeply rooted that Henry VIII. caused his Minister (Wolsey) to be tried for having spoken into his majesty's ear; he accused him of an attempt to transmit syphilis to him through the agency of his breath. Sydenham and Cullen believed that contagion was effected by vapors rising from the human body. However, the practice of variolization and vaccination clearly demonstrated that the viruses were not always volatile. The profession was thus led, at the beginning of the nineteenth century, to admit two orders of contagion: one volatile, that is, the air charged with putrid vapors; the other fixed, multiplying within the organism.

What, however, is the nature of this fixed virus? Fracastor had already compared the development of disease to putrefaction, without, of course, suspecting the animate origin of the latter process. He thought that germs developed and served for the propagation of the malady. The same idea was taken up by Henle (1840), who believed that contagious diseases were due to organic particles emanating from the living organism and preserving their pathogenic power. Ch. Robin's theory hardly differed from the preceding one: "Virulent diseases are those in which the fundamental organic substance or substances of one or of all the humors have undergone a specific modification, which modification is transmitted to organic substances themselves and then to the organized substance of any other living being. . . . As to the creation of the virulent state, it is the same phenomenon as the one that occurs for the formation of the organic substances themselves by isomeric catalysis.[1]" That

[1] Littré et Robin. Dict. de méd., art. Inoculable et Virulent, Paris, 1878, 14th ed.

normal substances should undergo analogous alterations on coming in contact with some modified organic matter was not far from conceivable; but the doctrine fails to explain the appearance of the modified state. It does not offer an acceptable theory by comparing the development of virulent diseases to the formation of organic substances. This brought into the domain of pathogenesis the current ideas upon spontaneous generation. Even the great discovery of Villemin did not suffice to overthrow the erroneous theories, as it only established the transmissibility of tuberculosis from sick to healthy individuals. Although of great importance from the standpoint of hygiene and prophylaxis, it did not reveal the nature of the pathogenic agent.

Even previous to this epoch, however, certain minds were impressed by the analogies existing between the development of infectious diseases and that of animals and plants. It was merely a comparison, but was destined to be a highly fertile one. Solid arguments, however, did not appear until the beginning of the nineteenth century. By a sort of divination, some minds began to perceive the truth. Hildebrand, in his book on contagious typhus (1811), showed that miasms spread and multiplied like the germs of living beings. About the same period J. Hamean, a country physician, to whom is due one of the first observations of the transmissibility of glanders from the horse to man, argued that virulent matters possessed a life principle, since they acted like parasitic insects. He further stated that there is an antagonism between certain viruses, such as variola and vaccinia, and transitory viruses, such as scarlatina, and the bodies which they leave, since they attack them no more—*i. e.*, confer immunity. It must be admitted, therefore, that viruses produce within the body excrementitious substances which, so long as they are not eliminated, inhibit their action. Hamean thus perceived the mechanism of acquired immunity as it is admitted at present.[1] Budd asserted (1850) that cholera was transmitted by germs, and, in 1870, he assumed that living organisms represented the specific cause of contagious diseases. Bouillard accepted the same idea, and Trousseau, in a famous lecture, showed that infectious diseases were transmitted by living germs: "The facts of contagion," said he, "would thus materially be explained, if the presence of these spores in the atmosphere could be discovered. To attain this result one should

[1] J. Hamean. Etudes sur les virus (1836–1847). Edition preceded by a preface by Prof. Grancher, Paris, 1895.

follow the path traced by M. Pasteur and proceed with the same experimental ability and patience."[1] H. Gueneau de Mussy (1878), in his preface to the translation of Murchison's book on typhoid fever, pleads in favor of the parasitic doctrine and points out the respective parts played by the seed and the soil.

However, these pathogenic conceptions, which were arrived at by reasoning, were to be followed and confirmed by bacteriological researches. The first step was to attribute infections to relatively highly organized parasites. Varron and Columelle speak of diseases engendered by insects spread in the air. In the sixteenth and seventeenth centuries analogous ideas were developed by various observers. Infusoria were described by Languis for measles; by Zacutus for smallpox; by Kircher for the plague. On the other hand, Lancisi, Réaumur, and Linné supported with their great authority the animate nature of contagions. Deidier admitted the agents of syphilis to be worms; Goiffon (of Lyons), in 1721, believed that invisible insects transported the plague. This coarse parasitism reached its height with Raspail.

The true pathogenic agents had, however, been seen as early as 1850. In that year Rayer communicated to the Société de Biologie observations which he had made with Davaine upon the blood of sheep infected with anthrax. By examining under the microscope a drop of blood derived from the dead animal, they had seen "minute filiform bodies about twice as long as the diameter of a red blood corpuscle. These little bodies presented no spontaneous movements." Pollender and Brauell rediscovered these same elements. Delafond, in 1860, considered them as plants and attempted to cultivate them, and even endeavored to demonstrate the spores. He failed at the latter point. The existence of anthrax spores was to be demonstrated sixteen years later by Robert Koch.

In spite of the important discoveries which enriched the history of anthrax, no one had understood the pathogenic rôle of the rods, to which a prognostic value alone was attributed. The true conception was gradually attained in an indirect manner by the study of fermentations. Rhazés, Hoffmann, Bressy, and others compared infections to fermentations, a comparison of great interest. Unfortunately, however, the cause of fermentations was just as little understood as was that of infections.

[1] Trousseau. De la contagion. Clinique méd. de l'Hotel Dieu, t. i p. 593–622.

The fact is that an erroneous doctrine, prevailing since the time of Aristotle, prevented advance along this line. Reference is here made to the idea of spontaneous generation. Redi, in 1668, was the first to rise against this dogma. Transporting the problem to experimental ground, he showed that the larvæ of flies were not born spontaneously through putrefaction of meat. When the insects were prevented from depositing their eggs no larvæ could develop.

Soon after, in 1678, van Leeuwenhoek discovered in infusions minute animals which Wrisberg, in order to indicate their origin, named infusoria. Van Leeuwenhoek admitted that these minute beings floated in the atmosphere, but his view was not acceptable to all, and his researches became the subject of memorable controversies, principally between Needham and Spallanzani. The latter proved by admirable experiments that infusions remained sterile when well protected from the germs of the atmosphere.[1] This discovery was confirmed and completed by Schulze and Schwann at the beginning of the nineteenth century. Finally, in 1837, Cagnard-Latour demonstrated the numerical and ponderable increase of yeast in the course of the fermentative process and established its animate nature. Still, Liebig's school persisted in attributing fermentation to the action of some decaying substance.

Such was the state of the question when Pasteur's researches on the lactic acid ferment (1857), the alcoholic ferment (1860), and finally, on some anaërobic, viz., butyric ferment (1861), were successively published.

Pasteur's researches on silkworm diseases (1865–1870) may be considered as the fundamental work from which the era of the new discoveries and doctrines dates. Unfortunately, these researches were ignored or uncomprehended by the medical world. Davaine, however, had surmised that disease as well as fermentation depended upon animate agents, and accumulated a considerable amount of experimental facts in support of this conception.[2] In spite, however, of the admirable investigations of Davaine, and the discovery of

[1] Spallanzani. Observations et exp. faites sur les animalcules des infusions. Œuvres complètes (Trad. Senebier), 1787, t. i. Observations et exp. sur l'origine des petites plantes des moisissures. Ibid., t. ii. p. 286–309.

[2] Davaine. Recherches sur les infusoires du sang dans la maladie connue sous le nom de sang de rate. Comptes rendus, 1863. Davaine published a great number of notes inserted into the C. R. of the Academy of Science, Academy of Medicine, and Society of Biology. They are collected in l'Œuvre de Davaine, Paris, 1889, t. i.

anthrax spores by Koch,[1] the parasitic theory of infectious disease had few adherents. Further opposition was rendered impossible, however, when Pasteur,[2] by the method of cultures, demonstrated beyond all doubt that anthrax is caused by the bacillus anthracis as scabies is caused by the acarus scabiei. A few years later bacteriological doctrines received official sanction at the Paris Faculty of Medicine by Prof. Bouchard, who was the first to study the rôle played by animate agents in the genesis of infections.

This was in 1880 and 1881, when reaction was intense. Opposition gradually gave way to successive discoveries which established beyond dispute that infections are due to parasites—some vegetable, others animal, most of them of a bacterial nature.

Classification of Infectious Agents.

Pathogenic Bacteria. For reasons already referred to we cannot, as do some authors, regard "infectious" and "bacterial" disease as synonymous. Admitting, however, the considerable pathogenic rôle of bacteria, we shall begin the history of pathogenic agents by a study of them.

At present bacteria[3] are generally considered as belonging to the family of algæ, and not, as was formerly believed, to that of the fungi. Hence, the name schizophycetes[4] would be more suitable than schizomycetes,[5] generally employed since Naegeli's time.

From a purely medical standpoint, bacteria are divided into two groups under the names saprophytic and pathogenic, according as they develop in dead or in living organisms. Though highly important, this division is not complete. We think it is well to add a third group—that of *parasitic bacteria*—which vegetate upon living organisms without inflicting any appreciable harm. It is also to be

[1] R. Koch. Die Aetiologie der Milzbrand-krankheit. Cohn's Beitr. zur Biol. der Pflanzen, 1876.

[2] Pasteur, Joubert, Chamberland et Roux. Numerous notes published in the Comp. Rend. of the Academy of Science, beginning with 1877.

[3] Bacterium (from *βακτήριον*, a little stick, diminutive of *βακτήρια*, a stick, staff, plural, *bacteria*) is a general name applied to microbes entering the group of schizophytes. The term bacterium should not be employed as synonymous with microbe. The latter (*Μικρος*, small, *βιος*, life) is used to designate all microscopic beings of vegetable or animal nature.

[4] Schizophycetes (*σχίζειν*, cleave, split; *φυτον*, plant), algæ which multiply by division or fission.

[5] Schizomycetes (*σχίζειν*, to cleave, *Μύκης*, pl. *Μύκητες*, a fungus), fungi which multiply by cleavage or fission; hence fission fungi.

remembered that the same bacterium may sometimes be a saprophyte and at times a parasite, and on other occasions rise to the rank of a pathogenic agent. It is true that there are bacteria which, thus far, have always seemed to be devoid of virulence, and their cultures injected into animals, even in large doses, induce no disturbance. There are, however, others which are capable of passing from the state of a saprophyte to that of a pathogenic agent; and, reciprocally, the majority of infectious bacteria may have a saprophytic life. It is not, therefore, indulging in pure hypothesis to admit that microbes have accidentally become morbific and that it is by accident that they pass from a saprophytic to a pathogenic life.

In view of these facts, some preferred to classify microbes according to other characters, notably their biological properties. Pasteur, who attached little importance to morphology, considered fermentative processes of far greater consequence. He believed that by studying the modifications which microbes produced in well-defined products it was possible to reach a sure classification. Fermentative action, however, has no fixed characters. Several different bacteria may give rise to the same products. Moreover, within a well-defined species are found varieties enjoying similar fermentative powers. Finally, by means of successive cultures the action upon media may be modified.

There is, however, an action which is considered by most authors to be of considerable diagnostic importance, viz., the peptonization of gelatin. Hence, the majority of bacteriologists divide microbes into those which liquefy gelatin and those which do not. This character is evidently of real interest, but there is no reason for attributing to it an absolute value sufficient to separate species which, in other respects, seem to be closely allied.

A natural classification of bacteria requires cognizance of the greatest possible number of characters. Such an attempt, at the present stage of the science, is premature. It is better to be guided by some objective character of sufficient constancy and appreciable without much difficulty. Accordingly, the majority of authors have taken morphology as a basis.

Without enlarging upon all classifications that have been proposed, the author believes that bacteria may be grouped in the following simple manner:

Cocci	Monococcus. Diplococcus. Tetracoccus. Streptococcus. Staphylococcus. Merismopedia. Sarcina. Leuconostoc. Ascococcus.
Bacilli (rod-shaped)	Bacterium. Bacillus. Leptothrix. Beggiatoa. Crenothrix. Cladothrix.
Curved bacteria	Vibrion. Spirillum. Spirochæta.

Cocci (κόκκος, berry, grain) are round elements, almost always non-motile and sporeless. According as the elements are isolated or agminated, they are called monococci, diplococci, and tetracocci; when in the form of a chain, streptococci, and when presenting the shape of grape bunches, staphylococci. These divisions are of no great importance, since the same species may appear under several aspects. It is true, however, that it assumes by preference one of these aspects which serves as its characteristic feature.

The merismopediæ are constituted by cells or plates arranged on a plane. In sarcinæ the mode of division is peculiar. It has three planes of division. Leuconostoc and ascococci are of little importance from a medical standpoint.

The group of rods contains, in the first place, the bacteria and bacilli. The former are short and often ovoid in form; the latter are cylindrical. This distinction, however, is gradually being displaced, and the term bacilli is now almost universally employed.

The leptothrix occurs in the form of a more or less segmented filament. The crenothrix presents the same aspect, except that it is surrounded by an envelope. The cladothrix is characterized by the presence of lateral filaments, so that some authors have taken it to be a higher organism than the bacteria and confounded it with the streptothrix. In an important contribution, Sauvageau and Radais demonstrated that in cladothrix there are no real branchings. There are only new elements, produced by fission, which remain attached to each other. They constitute a colony, not an individual. It is important to emphasize this point, since authors often confound the two, and it is not clear whether they refer to cladothrix or streptothrix.

The third and last group is composed of curved elements. Some have the shape of a comma or of an S. These are the vibrios. Others present the form of spirals. When the screw-like turns are few in number and less close, the elements are called spirilla; when the contrary is the case, they are sometimes designated as spirochætæ.

It is often a matter of difficulty to clearly indicate the respective value of characters attributed to various groups. For instance, it is generally admitted that there are numerous analogies between the colon bacillus, the pneumobacillus, and the typhoid bacillus. One might add even the bacillus of pseudotuberculosis of rodents. Should these various types be considered as distinct, though allied, species, or, on the contrary, do they represent varieties that may be transformed into each other? The delicate question has long been the subject of controversy. Moreover, the colon bacillus and pneumobacillus vary extremely in form, biological properties, and pathogenic potency. We are, therefore, led to presume that these species comprise numerous varieties which have often been described as new species.

Over two hundred pathogenic bacteria are actually known. They may, in this respect, be divided into two groups according as they produce a well-defined disease or give rise to various pathological processes. Such a division is in harmony with the expressions "specific" and "non-specific." Taking morphology into account at the same time, we reach the following classification in which the principal species alone are included:

NON-SPECIFIC BACTERIA.

Micrococci.

Pyogenic staphylococcus	aureus. citreus. albus.
Streptococcus	very numerous varieties.
Pneumococcus (*Streptococcus pneumoniæ*)	
Tetragenus	albus. citreus.

Bacilli.

Colon bacillus	B. lactis aërogenes. B. neapolitanus. B. pyogenes fœtidus. B. enteritidis. B. endocarditis griseus. pyobacillus Fischeri. B. cavicida. septic bacillus of the bladder. pyogenic bacterium. paracolon bacillus.
Pneumobacillus	B. of rhinoscleroma. *B. hominis capsulatus.* *B. capsulatus septicus.* *B. endocarditis capsulatus.*

B. of pittacosis.
B. of hemorrh. septicemias.
B. septicus putidus.
Proteus vulgaris . . . . . { *Proteus mirabilis.* / *Proteus pleomorphus.* / *Proteussepticus.*
B. of dysenteriform enteritis
B. pyocyaneus . . . . . { α. / β.
Leptothrix buccalis

SPECIFIC BACTERIA.

Micrococci.

Gonococcus
Diplococcus intracellularis meningitidis
Micrococcus of mumps

Bacilli.

B. anthracis . . . . . several experimental varieties.
Diphtheria B. . . . . { pseudodiphtheria B. (?) / short B. (?)
B. of glanders
Typhoid b.
B. of influenza
Tubercle bacillus (perhaps to be placed among the streptothrix) . . . { human B. / B. of the gallinæ. / B. of fish.
B. of leprosy.
B. of pseudotuberculosis.
B. of bubonic plague.
B. of yellow fever.
B. of soft chancre.
B. of tetanus.
B. of gaseous gangrene . . . . B. of symptomatic anthrax.
B. of rheumatism.
Spirillus of recurrent fever.
Vibrio of Asiatic cholera.

The Infectious Fungi. As already stated, infectious diseases may be caused by plants more highly organized than schizophycetæ.[1] The streptothrixæ will first be mentioned. Of these a dozen are at present known, several of which are pathogenic. More frequently, however, they induce local lesions only. There are in this group four plants which are capable of giving rise to genuine infectious diseases.

In the first place, there is *Nocardia farcinosa*, which produces a malady known as *farcina bovidæ*. It was discovered by Nocard, who at first considered it to be a cladothrix. It causes in bovidæ lymphagites and suppurating adenites, which are not to be confounded with true glanders, a disease from which bovidæ are immune.

Oöspora asteroides, discovered by Eppinger (1891) in a cerebral abscess, was again found by Almquist in a case of meningitis, by Ferré and Faguet in an abscess of the brain, by Sabrazes and Rivière in a cerebral abscess and in a suppurating infarct of the kidney.

[1] For the study of these diseases consult: W. Dubreuihl, Les moisissures parasitaires de l'homme et des animaux supérieurs, Arch. de méd. exper., 1891, p. 428 and 566. Blanchard, Les parasites végétaux, Traité de path. générale, 1896, t. ii. p. 811.

Actinomyces (*Nocardia bovis, streptothrix actinomyces, oöspora bovis*), the most important agent of this group, is pathogenic for both man and various mammalia, notably bovidæ. It may be considered as the type of higher agents capable of producing infectious diseases.

Phycomyces are fungi which constitute a transition with the algæ. They include oömyces and zygomyces. Among the former is found leptomitus, which is pathogenic for insects and is also encountered in man. In the majority of instances, however, it is a simple parasite.

Zygomyces comprise the entomophthoræ and the mucedinæ. Furbringer reported two cases in which the pulmonary foci were due to *mucor mucedo*. The case reported by Paltauf[1] is more interesting: The patient, a man, fifty-two years of age, succumbed nine days after his admission into the hospital with very serious general symptoms: fever, icterus, diarrhœa, tumefaction of the liver, and spleen, typhoid state, and coma. At the necropsy there were found intestinal ulcerations, foci of pneumonia, cerebral abscesses, and suppurative laryngitis and pharyngitis. These various lesions were due to a parasite which appeared to be the mucor corymbifer. Experimentation further demonstrated that this vegetable was pathogenic for animals (Lichtheim).

The mycomyces are fungi of a low order comprising an important group, viz., the ascomyces. In fact, it is in this group that yeasts are classed. Experimentation demonstrated the existence of a great number of yeasts that are pathogenic for animals. A few observations tend to establish the same to be true with regard to man. This subject will be discussed in a separate chapter.

Finally, there are the perisporiacæ which comprise aspergillinæ. These frequently produce lesions in the respiratory organs of birds (A. C. Mayer, Robin, Bouchard, Hayem, etc.). *Aspergillus fumigatus* may cause various lesions in man, such as cutaneous suppurations, a special form of onychomycosis, suppurations of the cornea, or lesions in the ear (otomycosis). In the latter case other parasites may also be encountered such as *aspergillus nigricans, aspergillus flavescens, aspergillus nidulans,* eurotium repens, etc.

Such are the principal mycoses observed in man. Their number is not considerable, as may be seen from the following list representing the main vegetable agents thus far discovered:

[1] Paltauf. Mycosis mucorina. Ein Beitrag zur Kenntniss der menschlichen Fadenpilzerkrankungen. Virchow's Archiv, 1885, Bd. cii., p. 543.

Oöspora asteroides (Streptothrix and Nocardia).
" *bovis* (actinomyces).
" *maduræ.*
Mucor runcedo.
" *corymbifer.*
Oidium albicans (Endomyces albicans, Vuillemin).
" *subtile.*
Aspergillus fumigatus.

I have excluded all those vegetable agents which behave in man as simple parasites. For the present it is sufficient to have shown that plants other than bacteria are capable of producing infections in man.

Infectious Protozoa. Infections due to protozoa are extremely frequent in the lower vertebrates, fish, the batracian, and in vertebrates. The same is probably true with regard to man and higher vertebrates, as some recent researches tend to demonstrate.

Of the four classes of protozoa, two only are of interest to us: the rhizopodes and the sporozoa. Among the former are the amœbæ, of which three varieties are met with in man. These are designated according to their seat, as *A. gingivalis*, *A. vaginalis* or *urogenitalis*, and *A. intestinalis*. The last is undoubtedly the most important. Numerous contributions tend to demonstrate that it is the causative agent of an important variety of dysentery and even of certain abscesses of the liver. Several observations have been reported in which amœbæ alone were found in hepatic suppurations consecutive to dysentery. The author published, with Dr. Peyrot, a case of this kind. It may, however, be presumed that ordinary pyogenic microorganisms existed at a certain moment and finally disappeared. Experimental pathology must, therefore, be resorted to in order to secure further information as to the pathogenic power of amœbæ. Marchoux succeeded in producing serious dysentery and hepatic abscesses in cats by introducing dysenteric dejecta into their digestive organs. These symptoms do not appear when the same dejecta are employed after subjecting them to a temperature which kills the amœbæ without affecting the accompanying bacteria.

The sporozoa comprise several groups, among which are found myxosporidia, sarcosporidia, and coccidia. The importance of the last-named group is constantly tending to increase. They are frequently met with in the liver of rabbits, where they invade the biliary passages and induce epithelial and connective tissue proliferations. Malassez encountered forms resembling the so-called colloid cells of epithelioma, the particular granula of *molluscum*

contagiosum and of vegetating follicular psorospermosis. These results are evidently of great importance in favor of the coccidian theory of psorospermosis and cancer, but the question is far from settled.

There has been described under the name *coccidium hominis* a parasite giving rise to intestinal ulcerations and often to a fatal cachexia. The karyophagus hominis of Podwyssotski induces pigmentary atrophy of the hepatic cells and secondarily gives rise to proliferation of the interstitial tissue.

Sporozoa also comprise the group of gymnosporidia of which, from the standpoint of infectious pathology, *plasmodium malariæ* is of chief importance. As is well known, this parasite, discovered by Laveran in 1881, is the cause of malarial fever.

Finally, should trichinosis be considered an infectious disease? The symptoms are evidently serious enough to deserve this denomination. In its first stage it develops like a true infection, and, in fact, it is most frequently confounded with typhoid fever. Be that as it may, the essential point established is the fact that there are infections due to animal microbes, and if doubt as to some instances is still possible, there can be none with regard to malaria—the disease which all clinicians consider infectious and of which the animal origin was demonstrated beyond all dispute by Laveran's great discovery.

CHAPTER II.

GENERAL CHARACTERS OF PATHOGENIC BACTERIA.

Polymorphism of Bacteria. Variability of Their Different Functions. Study of Ferments, Pigments, and Pathogenic Properties. Resistance of Bacteria to Destructive Agents. Action of Mechanical, Physical, and Chemical Agents. Action of High Pressures, Heat, Cold, Light, Electricity, Soluble Substances, and Antiseptics. Difficulty of Determinism in Microbiology.

Polymorphism of Bacteria. From the very beginning of bacteriology two contrary opinions appeared as to the value of characters peculiar to each species. Morphology was taken as a basis for classification. It was, therefore, necessary to determine whether the forms were or were not immutable. Cohn advocated monomorphism of bacteria, and Naegeli contended for polymorphism. On January 22, 1878, in a communication to the Académie de Médecine, Pasteur rejected morphological classifications, citing, as an illustration, the example of the septic vibrio, which, he said, "according to the media in which it is cultivated, assumes shapes, lengths, and sizes so diverse that the observer might believe them to be representatives of different species." In spite of the exaggerations of Zopf, polymorphism made considerable progress and found such advocates as Hueppe, Koch, Metchnikoff, etc.

In studying polymorphism it is necessary to distinguish cultures grown under eugenesic conditions from those grown in media or under influences unfavorable to their development. In the fomer instance morphological variation expresses an adaptation to slight or even hardly noticeable variations of environment; in the latter case it indicates a state of suffering and represents a modification of pathological order.

Polymorphism under Eugenesic Conditions, This must be studied in the living animal and in artificial cultures.

Pasteur indicated the variations of shape which the septic vibrio undergoes in the animal body. At the point of inoculation are found thick and short bacilli; in the peritoneum, and particularly near the surface of the liver, long, slender filaments are encountered. This result may readily be explained: The conditions of vegetation are

not the same in the more or less dense cellular tissue into which the injection is made and in the peritoneum where nothing hinders the development of the microbe.

By sowing the same microbe on different media dissimilar forms are often obtained. For instance, the bacillus of dysenteriform enteritis appears in the infected organism in the form of thick rods, resembling somewhat the bacillus anthracis, and measuring from 5μ to 6μ in length and from 1.3μ to 1.5μ in breadth. In bouillon they are more slender. In agar-agar they do not exceed 0.5μ by 2μ when the culture is twenty-four hours old; on the days following they are not more than 1μ or even 0.5μ in length and 0.5μ in thickness. Upon vegetables they are still shorter and more slender, and a few have an oval shape.

What may seem more curious is the fact that microbes may present different shapes in the same medium. In such cases the change is generally due to old age, the morphological variations corresponding to the various stages of their evolution. In other instances a modification of the medium is to be attributed to the life of the microorganisms. The bacteria absorb nutritive substances and produce ferments or excrete toxins which modify the constitution of the medium. The medium being thus modified, an adaptation on the part of the microbes is necessitated, resulting in morphological changes. So-called *involution* forms, which consist in swellings comparable to pears, clubs, bottles, etc., are observed, especially in old cultures in which the nutrient medium is exhausted or adulterated.

Polymorphism of the Buccal Tetracoccus. In studying the throats of patients suffering from simple or scarlatinal angina I have often found a microbe whose polymorphism may lead to confusion. This microbe, analogous to, if not identical with, tetragenus, is of very frequent occurrence in the mouths of scarlatinal patients. I have discovered it in 85 per cent. of such cases. The proportion is 69 per cent. in other sore throats, and 52 per cent. in diphtheria. This same microbe very often inhabits the throats of normal individuals and the buccal cavity of various animals, such as dogs, rabbits, guinea-pigs, and mice. At times it can be recognized by direct examination, that is, when it presents the form of typical tetrads surrounded with capsules. Its morphological variations, however, are considerable, and it not infrequently occurs in the form of diplococci or is arranged in small heaps of round elements in nowise characteristic. The polymorphism of the tetracoccus is also marked in

cultures. This morphological variability might, at first, lead to the belief that it is merely a question of accidental contamination. The writer has convinced himself that such is not the case, since by certain procedures it is possible to cause the microbe in question to pass from the zoögleic to the tetracoccic form, and *vice versa*.

The microbe of the author differs from the classical tetragenus not only by its polymorphism but also by its action upon animals. Unlike tetragenus, it is not pathogenic for rabbits, and very slightly so for mice. In sufficiently high doses, it produces very strange, nervous disturbances in rabbits.

It is, therefore, difficult to determine whether this microbe is identical with the classical tetragenus or not. In order not to prematurely announce its nature, the author proposes to provisionally designate it under the name of buccal tetracoccus (*tetracoccus buccalis*). At all events, the name tetracoccus is more in harmony with that of tetragenus in bacteriological terminology.

If, in spite of its great frequency in cases of sore throats, this microbe has not yet been brought to notice, it is owing to the fact that it develops poorly upon serum and that its polymorphism has caused it to be confounded with other microbes, notably with the streptococcus. This confusion can be avoided by taking into account the characters above indicated. In doubtful cases it is well to transfer a colony to gelatin. This medium, which is rapidly liquefied by the streptococcus, remains solid under the action of the tetracoccus.

Other examples might be quoted, but those above referred to suffice to show how numerous are the morphological variations presented by bacteria in the course of their development in the same medium. Analogous differences are also observed according as solid or liquid culture media are employed. In liquid media the microbes generally grow in length and group themselves in a different manner. This is not surprising. The study of plants of low organization, notably algæ, furnishes similar examples. Not to leave the field of pathogenic agents, it will suffice to recall *oidium albicans*. According as this plant is grown in agar-agar or in bouillon, oval or the filamentous forms predominate.

Polymorphism under Dysgenesic Conditions. The variations manifested by bacteria are still more curious when the latter are placed under conditions unfavorable to their development. In this connection it will be interesting to examine the influence of mechanical agents, and to determine, for instance, whether morphology is the

same when the culture is undisturbed or is agitated. As to physical agents, the rôle of heat alone has thus far been studied. It is known that the finest involution forms are obtained by placing the cultures in overheated media. The rôle of chemical agents has received more attention. Drs. Guignard and Charrin fully demonstrated the profound modifications presented by the bacillus pyocyaneus when cultivated in media to which antiseptic substances have been added. The bacillus then lengthens and assumes a filamentous form, or it rolls up into the shape of spirilla, or its size is reduced to such an extent as to resemble micrococci. These curious results were confirmed by Wasserzug's researches.

Under the same conditions many other microbes present morphological variations. In this respect the most remarkable microbe is the B. prodigiosus. When grown upon gelatin containing 2.5 to 3 per cent. of boric acid, it produces a magnificent spirilla having ten, twelve, and even sixteen or twenty turns; each turn of the spiral has a length of about 1.5μ; then on the fourth day involution forms appear which occupy the central part or the end of the spiral.

With the atypical variety I obtained in the same medium filaments varying in length from 15μ to 120μ and even 180μ. Toward the tenth day these filaments became segmented and gave rise to motile bacilli; at the same time involution forms appeared.

If a portion of these peculiar cultures is transferred to the usual media, colonies are obtained in which the microbes resume their normal form. The modifications imposed by antiseptics are, therefore, transitory. Wasserzug believed, however, that he had obtained an actual transformation and fixation of new characters. In reality, it is not possible to create by these procedures anything more than varieties comparable to the varieties observed in higher beings. In other words, we cannot transform the species.

As to the capsules which surround certain microbes, it must be stated that they are scarcely of any morphological and diagnostic importance, since they are quite inconstant.

Variability of the Functions of Bacteria. The experimenter may produce functional variations in microbes. He can modify their mode of reproduction, and by means of chemical agents he can create asporogenic varieties. Such, for instance, is the case with the bacillus anthracis.

Pasteur believed it was possible to characterize and classify

microbes by a study of their action upon fermentable substances. However, in this respect, also, the results are not constant. For instance, let us examine the action of the colon bacillus upon milk. The typical examples of this microbe coagulate milk because they attack the lactose, producing fermentation, and thus rendering the medium acid. There are, however, other varieties of colon bacilli, the paracolon bacillus of Gilbert, which do not coagulate milk. The author has observed a colon bacillus derived from a gangrenous pleurisy which did not at first act upon milk. On cultivating it in inert media, it was noticed that the medium was slowly rendered acid. It took a week to produce a little deposit of casein; two months later the same microbe completely coagulated milk in twenty-four hours. Here, therefore, is a variety that passed from the group of paracolon bacilli to that of the typical colon bacillus.

Similar results are obtained with yeasts. The transformation of sugar varies according to the aëration of the medium. The yeast plant, when living in the air, consumes free oxygen, multiplies rapidly and oxidizes the sugar almost without forming any alcohol. In its anaërobic life it is compelled to abstract oxygen from the sugar, which it then transforms into alcohol and carbonic acid.

Bacterial Ferments. The action of microbes upon sugar and albuminoid substances is also variable and differs according to the species employed, the age of the cultures, the nature of the medium, etc. Vignal called attention to the important rôle of pabulum furnished to bacteria. By adding certain substances to the culture medium the microbe can be made to secrete ferments which affect the substances introduced. There is only one secretion which seems never to undergo any variation, namely, that ferment which peptonizes gelatin. It is known that many authors consider the liquefaction of this substance as of importance in bacterial diagnosis. It is, in fact, one of the most stable properties and, consequently, one of those which are of considerable importance in classification.

Variability of Bacterial Pigments. Aside from the ferments, bacteria secrete various products, some of which may serve for identification of the species. Pigments are the most important of such products. A great number of microbes color the culture media yellow, red, green, and more rarely blue or violet. This chromogenic function is extremely variable. Certain microbes produce pigments in certain media. Thus the bacillus of glanders and the colon bacillus yield patches of a deep brown color when grown upon potatoes. The

colon bacillus, unlike the typical bacillus, produces a superb green color on slices of artichoke.

Under various circumstances certain chromogenic microbes may cease to produce pigment. For instance, *B. prodigiosus* when grown in agar-agar secretes a beautiful red pigment. If transferred to bouillon it does not color the medium; or to speak more accurately, certain cultures do not color bouillon, while others do color it red or rose.

By modifying the physical conditions of development, the production of pigments may easily be modified. Schottelius has shown that *B. prodigiosus* produces very little, if any, pigment, even in agar-agar, if the culture is kept in an incubator at a temperature of 100.4 F. (38° C.) or 102.02° F. (39° C.). Under these conditions the majority of colonies are white. If, however, this colorless culture be grown at a lower temperature, it becomes rose-colored, then red.

Analogous results are obtained by preventing the access of air. The author has shown that a culture of *B. prodigiosus* grown under oil remains colorless. When it is subsequently brought in free contact with air, color appears.

The most interesting modifications are those caused by addition of soluble or insoluble antiseptics to the culture bouillon.[1] Several of these substances first act upon the function of the microbe. In small amounts they hinder or arrest the development of coloring substance; in larger amounts, they hinder or arrest development; finally, their action may still be more marked and may kill the microbe.

In pursuing the researches on chromogenic bacteria I was able to prevent the production of pigment in *B. prodigiosus* by adding boric acid to the culture: 2.5 to 5 per 1000 suffices. Staphylococcus aureus produces white colonies when cultivated in gelose containing 3 per 1000 iodoform, or 0.6 per 1000 of carbolic acid. These amounts are close to sterilizing quantities, which are 3.5 per 1000 for the former substance, and 0.8 per 1000 for the latter. Finally, I have noted that extremely small amounts of antiseptics stimulate rather than hinder the chromogenic function. In the presence of a trace of corrosive sublimate *B. prodigiosus* produces a very intense red pigment.

These experiments are susceptible of infinite variations. The few

[1] Charrin et Roger. Des modifications qu'on peut provoquer dans les fonctions d'un microbe chromogene. Soc. de biologie, Oct. 29, 1887.

illustrations above referred to suffice to show the influence of the surrounding medium upon the chromogenic function of microbes.

Variability of Pathogenic Properties. Since the researches of Pasteur, it is known that microbic virulence may very notably be modified. If a pathogenic microbe is for some time cultivated in artificial media its virulence gradually diminishes and it sometimes falls to the rank of a saprophyte. Reciprocally, by passing it successively through living animals, it is possible to accustom the microbe to a parasitic life; in other words, it becomes *exalted*, and in many cases quite considerably. Pasteur's researches further established that a microbe that has been exalted for one animal species may be found weakened for another. It is also possible to modify virulence by making the cultures under special conditions, notably by subjecting them to high degrees of temperature, compressed oxygen, and chemical substances. These various processes enable us to create species of definite virulent power, or, as is said, fixed viruses. The *bacillus anthracis*, for instance, may be cultivated in such a manner as to be rendered incapable of killing the rabbit or of exerting any action upon even the adult guinea-pig; it can kill only the young guinea-pigs. By progressively graduated passages through a living organism it may recover its virulence.

It is, therefore, possible profoundly to modify the properties of bacteria, viz., to suppress their sporogenic, chromogenic, and virulent powers. Thus new varieties differing considerably from the original stock and not always surely convertible into it may be created. The functions thus abolished, however, are *fonctions de luxe*, since, notwithstanding these modifications, vegetation and reproduction may easily be accomplished. It is none the less interesting to note how contingent are the properties of microbes, and how difficult the determination of the species. The uncertainty of bacteriological diagnosis is so great that the same microbe has not infrequently been described under the most varied names. This variability in the characters of microbes is also referable to the fact that cultures are not and can never be uniform. For instance, if a colony of *bacillus prodigiosus* is diluted with a large amount of liquid and sown on plates, some of the colonies which develop will be red, others rose-colored, and still others white. If a colony apparently uniform—red or white—is diluted and sown, it will again produce dissimilar colonies. This simple experiment clearly demonstrates that all the microbes developing from the same stock are not equally capable of secreting pigment.

The results are identical, though less readily conceivable, with regard to the pathogenic function. All the individuals of the same culture do not possess the same power. It must, however, be recognized that by taking certain precautions we can diminish the differences, though we are unable to make them altogether disappear. Hence the necessity of carefully taking into consideration the sources of error connected with these experiments.

This variability of the elements contained in a culture fluid explains why when this fluid is submitted to the action of some destructive cause the number of microbes is first diminished, but the medium is not completely sterilized. Take, for instance, some pure bouillon culture and count the microbes by means of plates, and then submit the culture to the action of some destructive agent. As all the elements are subjected to the same harmful influence, simultaneous decline of vegetation, weakening of functions, and final destruction are expected. Such, however, is not the case. It will be seen that the number of colonies obtained on the plates diminishes successively, which proves that certain microbes, of weaker resistance, were the first to disappear; but others remain which, unless the conditions are too unfavorable, will overcome the dysgenesic conditions and become more or less perfectly accustomed to them. There occurs, therefore, a sort of natural selection.

Influence of Various External Agents upon Bacteria.

Influence of Mechanical Agents. The causes which arrest the development of and destroy microbes are mechanical, physical, or chemical.

The mechanical causes are represented by the movement of culture fluids. If the fluid is agitated the microbes do not develop or develop badly, but the fluid is not rendered sterile. By means of a simple apparatus invented by Dr. Gozard, I learned that repeated shocks in nowise affect the life of microbes. The microbes experimented upon—staphylococcus aureus, colon bacillus, streptococcus of erysipelas, sporulating or non-sporulating *bacillus anthracis*—were in no way affected by the mechanical action.

Action of High Pressures. The influence of pressure has been studied by various experimenters. The somewhat dissimilar results are referable to the diversity of the methods employed. The experiments of Regnard, Dubois, Certes, and Cochin demonstrated that

low beings resist very high pressure. The beer yeast is capable of bearing 300 to 400 atmospheres for several days without being destroyed. When submitted to 1000 atmospheres for one hour it becomes torpid and, an hour later, it is again capable of producing fermentation of sugar. The same is true of algæ and infusoria which have been subjected to a pressure of 600 atmospheres. The algæ germinate only after a week; the protozoa remain for some time motionless and then resume their movements. Regnard further learned that relatively higher organisms such as mollusks, crustaceans and leeches can endure 500 or 600 atmospheres without perishing.

As to bacteria, the effects of pressure vary considerably, according to experimental conditions. In fact, it seems demonstrated that compressed gases exert a very noxious influence upon several microbic species. According to P. Bert, oxygen, under a pressure of from 8 to 10 atmospheres, arrests putrefaction. The atmospheric air, under the same conditions, produces an analogous but less intense effect. In studying the *bacillus anthracis*, Prof. Chauveau showed that oxygen at 12 atmospheres weakens the vitality of this microbe and at the same time diminishes its virulence to such an extent as to transform it into a vaccine. Carbonic acid under pressure is equally harmful to bacteria. C. Fraenkel recognized that seltzer water contains no microbes. All species do not, of course, possess the same power of resistance. Hence the apparently contradictory results obtained by Sabrazes and Bazin.

The effect of 800 or 1000 atmospheres upon the four microbes (experimented upon in the author's first researches[1]) proving negative, the author thought it important to study the action of still greater pressures. He experimented with an apparatus by means of which the pressure could be raised to 2903 atmospheres, the cultures, as usual, being enclosed in rubber tubes. Since, however, the high pressure caused the water to filter through the walls of the apparatus, the author filled the cylinder, in which the tubes were placed, with oil. A special contrivance, set in motion by means of a motor engine, raises the pressure gradually, so that it takes ten minutes to attain 2903 atmospheres. This pressure, the highest that can actually be obtained, is kept up for two minutes; it is not possible to further prolong the experiment without danger to the apparatus. The pressure is then allowed to fall to the normal; this descent is rapid,

[1] Roger. Action of High Pressures upon Some Bacteria. Comp. Rend. de l'Académie des Sciences, Dec. 3, 1894; Arch. de phys., Jan. 1, 1895.

as it lasts but ten seconds. The latter fact is of considerable importance, for perhaps some of the effects obtained may be due to decompression.

Under these conditions the colon bacillus and *staphylococcus aureus* have hitherto suffered no modification; their cultures were as luxuriant after as before the experiment. Their functions were not even disturbed, since the staphylococcus preserved its chromogenic power.

The streptococcus was sown in agar-agar before and after compression. The tubes were placed in the incubator at 6 P.M. and examined at 9 A.M. the following day. Those which had received the normal cultures were covered with colonies; the others showed no growth. In the evening, however, they presented colonies one-third less numerous than the control tubes. Apart from these numerical differences, which remained the same the following days, there was no appreciable modification either in the appearance of the colonies or in the form of the microbes.

In conjunction with the culture experiments inoculations were practised upon rabbits. Ten drops of the culture were introduced under the skin of the ear. Two days after the rabbits which had received the streptococcus subjected to compression were attacked by erysipelas of the ear. The affection grew worse on the following days, then began to subside, and disappeared on the tenth or eleventh day. The controls presented no local lesion; they succumbed to a general infection five or six days after the inoculation.

A pressure of 2903 atmospheres (about 3000 kilogrammes per square centimetre) is, therefore, capable of killing a few streptococci. It induces in those which survive a sort of torpidity as expressed by a notable delay in development, and, what is of greater consequence, it diminishes their virulence to such an extent as to leave them the power to produce only a local and rapidly curable lesion.

The effects of pressure upon the *bacillus anthracis* are analogous to the above.

It may, however, be questioned whether the effects observed with the streptococcus and the *bacillus anthracis* are due to the increase of pressure. The rise of temperature caused by compression of the fluids may, perhaps, account for all these phenomena. Commandant Meillet, who has studied this problem, calculated that under a pressure of 2903 atmospheres (3000 kilogrammes) the rise of temperature was only 9.54° F. (5.3° C.). This is rather too high a figure, as it

assumes that all the *force is transformed* into heat. The thermal effect cannot, therefore, explain the action of pressure.

In order, however, to influence the life or functions of microbes enormous pressures far in excess of actual cosmic variations must be employed, since the pressure at the bottom of the sea is far less (500 or 600 kilogrammes). Consequently, it may be stated that changes of atmospheric pressure occurring on our globe play no rôle in the modification of the virulence of the microbes surrounding us.

Action of Physical Agents on Bacteria. As is well known, physical agents, especially heat and light, exert a harmful influence upon bacteria.

Action of Heat. Heat is daily employed for purposes of sterilization. All bacteria, however, are not destroyed at the same temperature. There are some that can live, develop, and multiply between 158° and 165° F. (70° and 74° C.). Globig found in the soil thirty species living between 122° and 158° F. (50° and 70° C.). Miquel, Olivier, Rabinowitsch, and Macfayden studied the thermophilic microbes found in hot spring waters and notably in sulphurous waters.

For the same bacterial species, sensitiveness to heat varies according to several conditions. The spores are more resistant than the adult forms. Heat is more destructive to the microbes when the latter are contained in a fluid medium than when in a desiccated state. Finally, the action of heat is considerably increased by the presence of air which produces oxidation unfavorable to bacteria.

Immersed in water at 140° F. (60° C.) the tubercle bacillus lives for twenty minutes; and in water at 158° F. (70° C.), for ten minutes. Boiling water at 212° F. (100° C.) kills it in five minutes. The same bacillus is capable of resisting a dry heat of 212° F. for several hours.

The influence of air is shown by Dr. Roux's experiments. When subjected to the combined action of air and a temperature of 158° F. (70° C.) the spores of *bacillus anthracis* die in sixty hours; when protected from air they live one hundred and sixty-five hours.

Resistance to cold is far more considerable. Ice contains numerous microbes. Dr. Pictet subjected bacteria to temperatures of —166° F. (—110° C.) and even —328° F. (—200° C.) without being able to kill them. Prof. D'Arsonval immersed some in liquefied air without causing them to lose their power to vegetate.

Action of Light. The influence of sunlight is at least as important as that of heat. It may easily be proved by the following experiment: A few drops of an anthrax culture are spread upon a gelatin plate, which is then covered with a glass upon which pieces of black paper are pasted. When exposed to light, development takes place in the protected parts, and the bacteria exactly reproduce the designs figured by the pieces of black paper.

This influence of sunlight is constantly at work in nature. Bacteria are speedily destroyed at the surface of the soil, while at twenty inches below the surface they find excellent conditions of resistance, and may retain their vitality for more than five months.

The results are similar for bacteria immersed in water.

Pansini introduced a few drops of an asporogenic anthrax culture into water which he then subjected to the action of the sun. The number of bacteria was primarily 2520 per cubic centimetre. At the end of twenty minutes the number was reduced to 130, and at the end of half an hour to 44 per cubic centimetre. After forty-five minutes there were none to be found.

Procaccini took sewer water containing 300,000 to 420,000 bacteria per cubic centimetre and subjected it to solar influence. At the end of the day the water was sterile.

The following is another experiment made under perfect conditions: The water of the Isar, before its entrance into the city of Munich, was examined by Buchner at different hours of the day. The highest figure was found at 4 A.M., as bacteria had increased during the night, and their number then reached 520 per cubic centimetre. The minimum was observed at 8 P.M. Exposed to the sun all day, the water contained no more than five bacteria per cubic centimetre.

The experiments of Marshall Ward tend to prove that light acts directly upon the anthrax spores, and that its action is inhibited when the plant is protected by means of a screen intercepting the blue and violet rays. Thus, as Downes, Blunt, Arloing, Buchner, and Frankland had already seen, it is the most refrangible rays which possess germicidal power. The orange and red rays do not disturb the development of bacteria.

As in the case of heat, the action of light is favored by the presence of air. Dr. Momont demonstrated that anthrax spores perish after forty-eight hours of insolation when they are in contact with air. *In vacuo* they live for one hundred and ten hours.

Light modifies the functions of bacteria at the same time that it affects their vitality. Anthrax is attenuated under its influence. The red bacillus of Kiel ceases to produce pigment, at times permanently, so that if it is sown in the shade, it does not recover its chromogenic function.

The study of the other physical agents in this connection is a matter of considerable difficulty. Hence, in the old experiments upon the effects of electricity the currents employed produced heat and electrolysis. The germicidal action was due, therefore, to thermal or chemical modifications. Those experimenters who have taken cognizance of these sources of error have not been able to detect any direct action of electricity upon bacteria.

Action of Chemical Agents. Those chemical agents which are capable of unfavorably affecting bacteria are called antiseptic agents. Among gases there is, for instance, ozone, of which, as is known, great quantities are often found in the atmosphere. Its action is very energetic, at least upon the adult forms. The asporogenic anthrax bacillus is killed under its influence in five hours, but the spores perish only after three or four days.

The antiseptics properly so called possess the very curious property of stimulating the functions of bacteria when employed in minute quantities. Under their influence the chromogenic microbes produce a greater amount of pigment. When the amount of the antiseptic is raised the chromogenic power declines and even disappears. Vegetation then becomes slow, is arrested, and finally the microbe perishes.

Carbolic acid is one of those most frequently employed. In solutions of 1 per cent. it kills the asporogenic anthrax bacillus in ten seconds. If the microbe is spore-bearing, life persists for thirty-seven days in a solution five times stronger.

In order to promote the action of antiseptics, it is advisable to raise the temperature of the medium. Here is a fact of considerable importance from a practical point of view. For purposes of disinfection, warm solutions should be used. Thus, while anthrax spores resist a 5 per cent. solution of carbolic acid at ordinary temperature, they perish in the same solution in two hours if the temperature reaches 131° F. (55° C.), and in three minutes if it rises to 134.6° F. (57° C.).

Determination of Pathogenic Species.

In order for a microbe to be considered as the true cause of a disease it must, it is said, fulfil the following four conditions: it must be present in all individuals suffering from the disease; it must not be found in other diseases; it must be possible to isolate and cultivate it; and, finally, it must reproduce the disease by inoculation of its cultures.

These rules are excellent, but cannot be accepted as absolutely exact, and they therefore require some discussion.

The first precept is, perhaps, the most immutable, and would seem to admit of no exception. In certain cases, however, the search for microbes may be fruitless without impairing the value of previous positive findings. The pathogenic agent is not necessarily disseminated throughout the organism. It is, therefore, possible to overlook it if cultures are not prepared from every tissue and fluid. Even in those cases in which numerous cultures are made the result may be negative for the reason that the pathogenic agent is destroyed before the time of examination, having left lesions or a special cachexia. Suppurations originated by microbes persist long after the extinction of the microbes. Analogous facts are matters of daily observation in experimental pathology. We inoculate a mild virus, the animal dies after a considerable length of time. At that moment the most minute examination, the most exhaustive series of cultures fail to reveal the microbe introduced. It has perished, but the post-infectious events have followed their course to a fatal termination.

Another cause of error results from the fact that the principal microbe may be accompanied by, and even be lost among, other microbes. Necropsy is generally practised too late to give reliable results, for during the agony various species of microbes, particularly the colon bacillus, pass from the intestine into the viscera, fluids, and tissues, and it is these microbes which are found at the necropsy. These germs develop in artificial media more readily than the specific microbes, and if they are of the pathogenic class, as is the colon bacillus, they may readily be mistaken for the cause of infection.

Even when examination is made during life microbic associations are apt to lead to error. In diphtheria, for instance, it is quite exceptional to meet with a case free from such associations. It is not strictly correct to speak of pure diphtheria. Those cases in which inoculation into serum gives rise, at the end of fifteen hours, to no

other than the colonies of Loeffler's bacillus are thus designated. If, however, the same culture is examined after a few days, a great number of other microbes are found. In certain instances of true diphtheria the specific microbe may be absent, having been destroyed by common bacteria.

Analogous statements may be made with reference to cutaneous diseases. Secondary infections play a very great rôle in all affections of the skin and in eruptive fevers. For instance, at a certain period, pustules of variola always contain a great number of microbes which have nothing to do with the cause of the disease. These common bacteria may at times even penetrate into the organism and considerably embarrass bacteriological study.

There are other clinical types in which microbic association is still more important, not to say indispensable. Such is the case in tetanus. The bacillus of Nicolaier is incapable of developing in healthy tissues. In order to be able to act, it requires the assistance of auxiliaries to reduce the resistance of the animal organism. The morbid focus, therefore, contains various microbes, but the tetanus bacillus alone secretes the poisons which reproduce in animals the characteristic phenomena of the disease.

Finally, in certain cases, the morbid centre contains several bacteria endowed with wellnigh similar properties. In such instances the doubt as to the respective share of each of them is unavoidable and legitimate.

The third law which has been cited will not detain us long. It is now recognized as a common truth that the relations existing between pathogenic agents and diseases are not such as they have been defined. It is scarcely necessary to recall that the streptococcus sometimes produces erysipelas, sometimes phlegmons, sometimes general infections, septicemias, and pyemias. In the beginning of bacteriological study facts of this kind seemed inadmissible. We were so used to our nosographic groupings that we hesitated to disturb them by etiological researches. The day is long past, however, when a constant relationship between disease and microbe was obstinately maintained. It is now admitted by all that one and the same microbe may give rise to most varied maladies. In order, however, to justly consider an animate agent as the cause of an affection, it is necessary to isolate, cultivate, and inoculate it. Here other difficulties are encountered. Certain beings visible under the microscope do not develop outside the organism and are not pathogenic

for animals. To cite the best-known example, such is the parasite of malaria. It is easy to understand, therefore, why Laveran's discovery was not readily accepted. Ten years of ardent discussion was necessary to convince the opponents.

Inoculation of the pathogenic agent—viz., the reproduction of the observed disease in animals—has led to such encouraging results, and its methods are so simple that it is resorted to on every hand.

The progress of experimental pathology has been most wonderful, but science is unfortunately overrun with uncertain and erroneous data, for which hasty and incomplete contributions are responsible. Moreover, owing to a natural tendency of the human mind, experimenters have asked of the laboratory more than it could give. Not contented with the information which it is capable of furnishing with regard to etiology, they wished to find certain and accurate indications concerning diagnosis, prognosis, and treatment. If, in certain instances, experimentation has responded to all that was asked of it, it has more frequently yielded uncertain and misleading results The fact is that there is no constant relation between the virulence of pathogenic agents for man and their action upon animals. Experimentation demonstrates this. A microbe exhalted for one species may be attenuated for another. While highly virulent for man, it may be harmless for laboratory animals.

Even when the virulence of a microbe undergoes no variation its effect may vary greatly, according to the previous state of the invaded organism. It is a matter of frequent occurrence that patients gravely infected transmit a mild infection, and *vice versa*. The history of variola offers numerous illustrations of this fact. Likewise, two individuals contract a venereal disease on contact with the same woman—*i. e.*, under conditions as identical as possible. In one of the cases, however, the infection is benign; in the other it pursues an alarming course.

These remarks are by no means intended to diminish the importance, but to indicate the difficulties of experimental researches. We shall endeavor to lay down rules which should guide bacteriological experimentation.

Role of Experimentation in the Study of Infectious Diseases. A first difficulty is the choice of the animal. The mouse, the guinea-pig, and the rabbit are the animals most frequently experimented upon; much less frequently the dog and the monkey are employed. Larger animals are difficult to manage and also too expensive. What,

however, complicates the problem is the fact that some diseases are exclusively human. Syphilis is of this number. In such cases the demonstration of the pathogenic agent becomes a matter of serious difficulty, as the unquestionable and final proof is lacking. The same remarks are applicable to other infections peculiar to man, such as mumps, typhus fever, and leprosy.

The impossibility of transmitting certain diseases to animals has compelled some authors to operate upon man. Long before the period of bacteriology attempts of this character were made, and science undoubtedly benefited by the inoculations of syphilitic virus. Although not many years have elapsed since that period, a higher and more just conception of our duty toward patients intrusted to our care has caused us rightly to condemn these criminal attempts. At the present day nobody would venture to inoculate the virus of syphilis, variola, or cancer. Should the subject consent to submit to such experiments, it would be our duty to refuse. If, however, an investigator believes he has discovered the pathogenic agent of some infection, he has the right to experiment upon himself.

When a microbe is inoculated into an animal, three results are possible: (1) the animal may be endowed with natural immunity and resist in spite of all efforts of the experimenter; (2) it may contract a disease altogether similar to that from which the microbe under study is derived—in which case, the result is perfect and convincing; (3) finally, it may present morbid symptoms which seem to have no analogy with those observed in man. In the latter instance the experimenter remains in doubt.

The last result may be illustrated by numerous examples. The pneumococcus, for instance, produces fibrinous pneumonia in man. The microbe is obtained from the exudate, cultivated, and then inoculated into a rabbit or a mouse, which dies in twenty-four or forty-eight hours without presenting any pulmonary lesion. It has succumbed to a genuine septicemia.

The result is evidently somewhat discouraging. It must, however, stimulate the experimenter to persist in his researches, for by changing the animals, by modifying the channel of introduction of the pathogenic agent, by producing various concomitant lesions, or by changing the culture medium, he may often obtain more conclusive results. Let us, therefore, lay down the principal rules of experimentation.

Inoculations are at times practised with virulent material taken

directly from a diseased individual. This method of procedure is now abandoned and is hardly ever resorted to since the introduction of cultures. It may, nevertheless, be of service in those instances in which the pathogenic agent is unknown. In hydrophobia, for example, direct inoculations only are made, and by means of certain procedures the virus is modified and graduated as easily as if it had been isolated and cultivated.

In some cases, even when it is possible to cultivate the microbe, it may be preferable to make inoculations with the diseased tissues, for, while the passage through artificial media modifies the virulence, it generally weakens it, and sometimes imparts to it particular characters. Inoculations in series are equally useful for strengthening a virus and for determining the virulence of a microbe in the organism. The last consideration guided me in my researches on avian tuberculosis. With Drs. Cadiot and Gilbert, the author inoculated directly into mammalia tuberculous products derived from birds, and, reciprocally, tuberculous products of mammalia were inoculated into birds. We were thus able to determine the real virulence of the bacillus. The results proved that we were right in so acting, since the employment of cultures gives rise to errors of interpretation.

In the majority of cases inoculations are made with pure cultures. This method alone furnishes reliable indications as to the nature of the pathogenic agents. It alone enables us to differentiate the microbes, to interpret their biological characters, and to modify their power and action upon the organism. The variations, however, which occur are not always due to the intervention of the experimenter. The virulence of a culture is sometimes lessened or vanishes for some unknown reason. This inconvenience has recently been remedied by modifying the culture media and by abandoning more and more the employment of bouillons. Animal fluids, serum, ascitic fluid, pleuretic effusion, defibrinated blood are made use of instead. These are sometimes mixed with bouillon or agar-agar, or the cultures are prepared within the living organism itself. Small capsules of collodion containing the microbe are introduced into the abdominal cavity. Diffusion of the organic fluids readily takes place through the membrane, which protects the pathogenic agent against the phagocytes.

Even under these conditions, however, the cultures do not always preserve their virulence or their uniformity. Just as with the higher organisms, which, when placed under apparently identical conditions,

are always dissimilar, the microbes contained in a medium are not all endowed with the same degree of vitality. Among the individuals swarming in a culture capsule some are more active or more pathogenic than others. It is very difficult, not to say impossible, to obtain perfectly uniform cultures. There is, however, much of interest in making attempts in this direction, since this individual variability of pathogenic elements is the cause of many contradictory results.

Determinism in Bacteriology. It is curious to note how little determinism in bacteriology is regarded. The reason is, perhaps, that determinism in this branch of research presents particular difficulties. To declare, however, that a bacterium inoculated into similar animals and under apparently identical conditions produces different effects is an avowal of impotence. That such should be the case with regard to man cannot be avoided. We must submit, so to say, to the caprices of clinical phenomena. We are victims of the chances and accidents of observation. In experimental pathology, however, we must endeavor to suppress the unforeseen and the inconstant. We must seek to obtain fixed and invariable results. This is, of course, a matter of great difficulty, for, while it is difficult to determine the phenomena, even in physiological experiments, the problem is far more complex in bacteriology. Here we combine two essentially variable factors. The animals, in spite of appearances, possess individual differences. On the other hand, the microbe, as a living being, possesses no immutable, well-defined properties such as are peculiar to a crystallized chemical poison. The result is that a microbe of variable action is introduced into an animal of variable reactions. The causes of uncertainty are thus added. While it is possible to interpret certain problems and to determine certain phenomena, in most cases this means to displace the unknown. For instance, let us follow the passage of the *bacillus anthracis* through the placenta. A certain number of pregnant guinea-pigs are inoculated; at the necropsy it is found that in some of the animals the bacillus has invaded the fœtus, but not in all. Such is the fact. Dr. Malvoz determined this by showing that the placenta does not permit the passage of organisms except when it is altered. If it remains intact, it acts as a perfect filter. Consequently, we are able to state precisely that the bacillus traverses the diseased placenta, but it does not pass through the intact placenta. It is evident, however, that the problem is only modified. In explaining a first

point a new one is introduced. It remains to determine the causes which permit or prevent localization of the bacillus in the placenta. When we become acquainted with them the phenomenon will then be elucidated.

The aim of the experimenter is, therefore, to reproduce in animals constant alterations and identical modifications. Next, he must vary one of the experimental conditions to obtain new effects. He will then be master of the phenomenon and be in a position to draw conclusions concerning the mechanism of infectious occurrences.

Through this procedure it has already been possible to solve certain questions in etiology and pathogenesis. This has been accomplished by modifying the local or general resistance of the animals by various means, such as intoxication, overwork, fasting, section of nerves, ligature of arteries, traumatism of tissues, etc. Morbid dispositions are created thus, and the results obtained lead to a better understanding of the mechanism of the pathological events.

This is not sufficient, however. A more profound study of the lesions is required. It is of the highest interest to note that not every part of a diseased organ is affected in the same measure. Along with diseased cells are found others in a perfectly healthy condition. Thus, after particularization of the species, of the race, and of the individual, particularization of the organs and tissues, and, pursuing the analysis still further, even particularization of the cells has been admitted. This fact, which is not without interest from a philosophical point of view, is the outcome of pathological studies. Normal anatomy and physiology could not lead us to this conclusion. On section of a normal organ or tissue all the cells seem alike. It is evident, however, that if they were all alike they should present the same alterations under the influence of the same pathogenic cause. It is difficult to explain why two neighboring cells placed apparently under identical conditions are differently affected. The age of cells may be responsible. These elements, according to the universal law governing all living organisms, succumb and are renewed unceasingly. Hence, it is impossible to determine whether two cells close to each other are not of very different ages. It is, then, readily conceivable that their resistance should vary considerably according to their ages. It must also vary in proportion to their functional activity, since it seems to be certain that particular parts of a gland rest while other parts are at work. If, therefore, for any of the

reasons above indicated certain cells are more affected than others, their descendants will differ from others in their morbid aptitudes or immunities.

These considerations will find numerous applications in the study of pathological anatomy and physiology. They will furnish us with a key to cellular lesions.

CHAPTER III.

ETIOLOGY OF INFECTIONS.

Division of Infections, According to Their Origin, into Heteroinfections and Autoinfections. Transmission by Direct Contact. Transmission through Air, Water, and Soil. Rôle of the Invertebrates. Transmission through Objects and Clothing. Disinfection of Apartments, Effects, Conveyances. Transmission by Plants. Transmission by Food. Autoinfections. Distribution of Microbes in the Normal Organism. Importance of Auxiliary Causes in the Development of Infections. Influence of Regions, Climates, Seasons. Influence of Race, Age, Sex. Rôle of Heredity and Innateness. Action of External Agents. Rôle of Poisons. Rôle of Fasting and of Fatigue. Development of Epidemics; Their Modification through Time and Space.

Heterointoxications and Autointoxications.

Infectious diseases may be due to two different origins: on the one hand, the pathogenic germs come from without, and their introduction into the organism is the evident cause of the morbid process: in other instances they are already present within the organism as simple epiphytes giving rise to no disturbance, but always ready to manifest their virulence on the slightest occasional cause. These divisions are indicated by the terms *heteroinfection* and *autoinfection*.

The recognition of autoinfections is of recent date and accounts for the numerous facts which were formerly ascribed to morbid spontaneousness. As soon as the microbes resume their pathogenic activity, however, they are capable of invading healthy persons and exerting their noxious power: the disease, born spontaneously, thus becomes transmissible.

A disease is said to be contagious when it can be communicated, either directly or indirectly, by a diseased individual to a healthy one. Although, in the majority of cases infecting and infected individuals belong to the same species, this is not always the case—man may be contaminated by animals.

In the case of direct transmission, contagion occurs in two different ways: either by contact or by inoculation. In the former instance the morbid germs derived from the infected subject invade the healthy organism through unbroken mucous membranes, generally through the respiratory passages or the alimentary canal. In the

latter case the virus is deposited, not upon the surface, but in the interior of the economy—*i. e.*, in a wound or abrasion. The disease is then said to be inoculated. It must be noted, however, that every contagious disease is inoculable, but that the reverse is not true.

Recent epidemiological researches tend considerably to limit the rôle played by air. They show that transportation is, as a rule, effected by persons and objects. Of the latter the best known are the utensils employed at meals, such as forks, spoons, and glasses; those used for the toilet, such as brushes, combs, and sponges. Clothing, bedding, books, letters, and coins and paper money must also be mentioned. Finally, in many cases in which propagation by air seemed to be demonstrated, it is now recognized that, in reality, transmission occurs through the agency of certain insects which ingest the microbes and then deposit them beneath the skin by true inoculation. Such is notably the case in malaria.

When ejected from the diseased organism, certain germs rapidly die; others often survive for a long time in water and soil, upon floors, walls, etc. We must, therefore, study these diverse origins of infections in their order.

Transmission of Infections by Contact. Let us first consider the simplest case—*i. e.*, transmission by immediate contact of healthy with diseased individuals. Here is an example of genuine inoculation which sometimes requires a previous erosion of tissues. At other times inoculation is effected through the intact epithelia, as occurs in venereal diseases: gonorrhea, soft chancre, and syphilis. Such immediate contact is not, of course, indispensable, since the virus may be deposited upon objects which serve for its transmission. The characteristic feature of this group is the fact that the pathogenic agents manifest little if any tendency to diffusion. They are not propagated by air or water and they do not vegetate outside the organism. It has been said that the gonorrheal virus embodied in pus particles may be spread by air, and in this manner epidemics of purulent ophthalmia invading a hospital ward are sometimes explained. It must be remembered, however, that, in most cases, minute inquiry demonstrates that propagation is due to immediate contact. The same is true of vulvovaginitis in children: the microbe is conveyed by the mother's contaminated hands, toilet articles, and particularly by sponges. Anthrax, glanders, and at times tuberculosis and actinomycosis may also be directly transmitted by accidental inoculation. The same should be true of hydrophobia,

although, in this regard, there is as yet no convincing observation. Bites by hydrophobic individuals have thus far never given rise to the disease.

In a second group may be classed those infectious germs which are capable of transmission to a distance through the agency of squamæ, urine, expectoration, etc. The cutaneous squamæ are often considered the agents of transmission of the eruptive fevers and erysipelas. For the latter disease, however, the mechanism of transmission is scarcely acceptable, since bacteriological researches demonstrate that the products of desquamation contain no streptococci.

The transmissibility of eruptive fevers varies according to the infection considered.

The germ of measles is contained in the oculonasal secretions and saliva, as was demonstrated by the successful inoculations made by Monro and Looke in the eighteenth century, and by Mayo in 1860. In accordance with these experiments, observation teaches us that measles is contagious before the stage of eruption, and soon ceases to be so, since five or six days after the appearance of the exanthem the germ seems to be destroyed. In very rare exceptions convalescents from measles have been known to infect healthy persons fifteen and even thirty days after the beginning of the disease.

The squamæ are generally believed to be the media for the transmission of the germs of scarlatina. According to recent researches by Dr. Lemoine, however, the morbid germs are found in the secretions of the throat, and the disease may thus be transmitted before the appearance of the eruption. By questioning scarlatinal patients I have found in several cases that the typical disease had developed in consequence of contact with an individual suffering merely from a sore throat.

As in measles, the germ of scarlatina is found in the throat and not in the squamæ. The latter may become the media of transmission in so far as they are apt to be contaminated by the saliva of the patient. It is also to be remembered that the virus of scarlatina is more persistent than that of measles. The period of forty days, fixed by the Council of Hygiene (of Paris), is generally sufficient, though contamination has exceptionally taken place after the expiration of this time. Unlike the scarlatina germ, that of measles possesses but slight viability and diffusibility. Two or three hours outside of the diseased organism is sufficient to destroy the virus.

Epidemiology of Smallpox. The study of smallpox strikingly illustrates the mode of propagation of epidemics of this disease.

The microbe of smallpox, by its great resistance, seems to closely resemble that of scarlatina, but it is far less diffusible. Its transmission through air has not been demonstrated. In many cases in which this mode of propagation was assumed inquiry established that a patient or some attendant had, in violation of instructions, trespassed the boundaries of isolation, or that disinfection of contaminated objects had not been thorough.

During the epidemic which raged in 1900 we received 928 patients in the Hospital d'Aubervilliers. Of this number, 246 had been contaminated directly by contact with individuals suffering from variola. We have established a rule that a smallpox patient must remain in the hospital for at least forty days. Those who need a certificate for resuming their work respect the rule, but others, under various pretences, leave the hospital too soon and spread the disease. The study of the epidemic of 1900 further shows that the poorer sections of Paris suffered most, since the rules of hygiene are not well observed by the inhabitants of these quarters. When there is a patient in a workman's family the neighbors often come to nurse the sick, and then return home or to work without taking any precautions. In one of my observations the janitress nursed a poor individual attacked by smallpox, and the devotion of this brave woman resulted in the transmission of the malady to the majority of the tenants.

The mildest cases are particularly dangerous for the public. An individual is seized with malaise, muscular pain, fever, and at times with rachialgia. He stays at home for three or four days. An eruption then makes its appearance: a dozen large papules resembling acne appear upon his face. At this time the patient feels well, and resumes his occupation. Not having consulted a physician, he is ignorant of the nature of the disease. It must also be remembered that many physicians are unable to diagnose variola since epidemics have become rare. Nevertheless, the failure of a physician to recognize smallpox has often been the cause of its propagation.

Epidemics in General. It seems that the study of conditions governing the development of epidemics in general tends more and more to reduce the rôle of transmission at a distance and to emphasize the importance of direct contamination. The latter mode is most often responsible for the infection of wounds. Though trans-

mission by air is possible, propagation is, in the majority of cases, effected through insufficiently cleansed instruments and hands.

Some twenty years ago, when infection of wounds was still frequent, I had the opportunity to observe an epidemic of erysipelas in a surgical ward. The first case was seen one morning. The following day a second case occurred, and others appeared on subsequent days. Transmission by air and the infection of the ward was assumed. On studying the course of the epidemic, however, it was noticed that only those patients had been attacked at whose bedsides the attendant surgeon and his assistants had stopped. The latter had received the germ of erysipelas from the first patient and conveyed it to the others. Those patients who had not been visited remained exempt. Here, then, is a series of facts contrary to the theory of the distribution of contagium through the air.

Infection may also be contracted by contact with diseased animals. In certain instances the virus is deposited directly in a wound; at other times by means of a bite, as in the case of hydrophobia; or by accident in handling diseased animals or cadavers. It has been asserted that scarlet fever is an infection of bovine origin and that it may be propagated by milk (Klein). Some authorities believe that all the eruptive fevers are of animal origin. Finally, an infection of parrots, which has recently been studied and is due to a bacillus related to the colon bacillus, is highly virulent for man. This infection is known as psittacosis.

Transmission of Tuberculosis by Contact. Of all infections tuberculosis is incontestably the most readily transmitted among different beings. Direct contamination of the healthy man by diseased animals is no longer a matter of doubt since the unity of tuberculosis in all animals has been admitted. While there are several varieties of Koch's bacillus the differences separating them are not of sufficient dignity to constitute specific characters. From a scientific standpoint, it is generally admitted that the digestive organs may be infected by ingestion of the flesh or milk of tuberculous animals. The frequency of such cases has not, however, been established.

Direct inoculation of tuberculosis seldom takes place. Several cases have been published concerning Hebrew children who became infected as a result of circumcision practised according to the rite, requiring the operator to arrest hemorrhage by oral suction. Modern researches have demonstrated the anatomical tubercle to be a gen-

uine bacillary tubercle. It is well to remember that direct inoculation may occur from bovidæ to man. The observation reported by Pfeiffer is a most remarkable one. Moser, a veterinarian of Weimar, wounded himself in making a necropsy upon a tuberculous cow. Six months later a cutaneous tuberculosis developed at the point of the cicatrix. He died from pulmonary tuberculosis two and a half years after infliction of the wound. Tscherning and Ponfick have cited similar cases. The researches of Verneuil and of Fernet have fully demonstrated the transmissibility of tuberculosis by sexual intercourse. Cornil and Dobroklonsky produced tuberculosis in guinea-pigs by injecting bacilli into their vaginal canals.

Transmission of Infections through the Air. After the contagious elements have passed out of the diseased body they may be dispersed by the air, transported by water, and reside in the soil, awaiting an occasion to invade a new organism.

Transmission by the air, although not of such frequent occurrence as was formerly believed, is, nevertheless, undeniable. The air contains a great number of microbes, as is shown by the following figures obtained by Miquel. These figures demonstrate the considerable variations observed in different localities:

On sea, at 100 kilometres from the coast	0.6
Altitude of 2000 metres	3.0
Summit of the Pantheon	200.0
Observatory of Montsouris	480.0
Rue de Rivoli	3,480.0
New houses	4,500.0
Sewers of Paris	6,000.0
Old houses	36,000.0
Hotel Dieu	40,000.0
Hôpital de la Pitié	79,000.0

In perusing this table it is surprising to note that the air of sewers does not contain many more microbes than that of a new house, and contains one-sixth as many as the air of an old house. The reason for this is that the innumerable bacteria residing in the water cannot enter the air. This has been demonstrated by experiments: a current of air passing over a contaminated liquid does not take up microbes.

The various figures above given have but a relative value. Considerable variations occur each day in the same locality. The number of microbes increases when a violent wind raises the dust, and diminishes after a rain which sweeps them down toward the soil. During the hot season the microbes increase. According to Dr. Miquel, the

average number of bacteria contained in the air of Monsouris is 170 in winter, 295 in spring, 345 in summer, and 195 in autumn. The highest figures were found in July and the lowest in December.

It has generally been thought sufficient to count the number of microbes in the air without ascertaining the proportion of pathogenic agents. However, Ullmann detected staphylococci in the air of a surgical ward, and Eiselsperg and Emmerich found streptococci. The latter microbe seems to be quite widely distributed in the atmosphere, or at least a variety of it is quite frequently met with in decaying substances. It has also been demonstrated that air may convey the contagium of diphtheria, typhoid fever, and the eruptive fevers. As already stated, however, this is seldom the case. Even influenza does not attack those persons who have not been in contact with those suffering from the malady, and, although its propagation is often rapid, it is not any more so than our means of communication. Epidemics are engendered not by the air but by the agency of individuals.

Transmission of Tuberculosis by Inhalation. From a bacteriological standpoint, the air expired from the lungs of a tuberculous patient is pure, since it contains no tubercle bacilli or any other microbe. The real danger resides in the expectoration. Protected by the organic particles in which it is incorporated, the bacillus retains its vitality in the dried sputa for a long period and is distributed far and wide. The protected bacillus is more dangerous than the free microbes, because the animal and vegetable detritus containing it act as foreign bodies and give rise to inflammatory reactions which favor "tuberculization."

Numerous experiments have proved that inhalation is a far more certain mode of contagion than ingestion. In this connection, Tappeiner's researches upon dogs leave no room for doubt.[1]

It is not correct, however, to say that the bacilli are carried by the dried sputa alone. The researches of Fluegge and his disciples, which have been confirmed by Moeller, have established that a consumptive, when speaking or coughing, projects about him a sort of microscopic spray of mucus and saliva charged with tubercle bacilli. The persons surrounding him are thus exposed to the danger of contracting the disease.

[1] Tappeiner. Ueber eine neue Methode Tuberculose zu erzeugen. Virchow's Arch., 1878. Neue exp. Beiträge zur Inhalationtuberculose. Ibid., 1880.

Conveyance of Infection by Water. The transmission of infectious diseases through the agency of water is far more frequent than by means of the air. This fact was known to the ancients, who used aromatic infusions as beverages, thus employing a very rational method of sterilization. In passing through the soil, water frees itself of microbes. Spring water, therefore, when taken at its source, is often absolutely sterile. For this to occur, however, water must percolate through porous strata. When it filters through calcareous strata, making its own little channel, it retains its microbes. Such are the waters of Avre and Vanne, which supply Paris.[1] As soon as it enters upon its course, spring water begins to acquire bacteria. Even hot mineral spring water contains bacteria.

It is readily understood that bacteria become more numerous when a water-course traverses a city. We must remember, however, that running water purifies itself quite rapidly. The following figures are convincing: The water of the Izar before its passage through Munich contained 305 bacteria per cubic centimetre. At its exit from the city, after having received the contents of the sewers, it contained 12,600 per cubic centimetre. Thirteen kilometres further down the figure is reduced to 2400 per cubic centimetre. This natural depuration is likewise effected in reservoirs. The water of the Thames, for instance, contains 1437 bacteria per cubic centimetre. It contains only 318 per cubic centimetre after its passage into a first reservoir, and 177 per cubic centimetre at its exit from a second. As already stated, the action of the sun is more powerful. Fewer microbes are found at 8 P.M. than early in the morning. The number may thus fall from 520 to 5 per cubic centimetre.

Epidemiological and bacteriological researches have led to prophylactic principles of importance. The water origin of typhoid fever, cholera, and dysentery seems to be definitely established. In regard to typhoid fever, the history of epidemics is at least as important as bacteriological researches, since it is difficult to separate and differentiate the colon bacillus from the typhoid bacillus, when these two microbes are present in the same fluid. The errors that have been made in this respect, however, have led to wise hygienic precautions. At the same time a more minute study of pathogenesis has developed new ideas concerning the origin and spread of infections. It has been questioned whether the rôle of water was not a complex one; whether,

[1] Thoinot. Les sources de la craie et la fièvre typhoide. Presse médicale, Feb. 14, 1900.

in addition to the possible presence of pathogenic agents, it was necessary to weigh the action of saprophytes capable of favoring their development. Authorities are now inclined to admit this theory with regard to cholera and typhoid fever. It accounts for those cases in which the disease attacked persons who had drunk from a reservoir polluted by percolations from cesspools. Typhoid fever has developed even when the matters were derived from individuals free from this disease or who had suffered from it a year before. At the end of so long a period the bacillus was certainly destroyed. In fact, according to the researches of Karlinski, it is known that the microbe does not survive in fecal matters for more than three months. This fact, which is often cited in support of the specific origin of the disease, seems rather to lead to a contrary conclusion.

Whatever mode is responsible, it is certain that water causes the majority of epidemics and explains their recrudescence in regions where the disease is endemic. In this connection nothing is more instructive than the researches of Drs. Brouardel, Chantemesse, and Widal. These authors showed that, in Paris, in 1885, 1886, and 1887, typhoid fever suddenly increased twelve or fifteen days after the population was supplied with river water, and disappeared as soon as spring water was again furnished.

The survival of germs in water has been studied by various authorities. Straus, Dubary, and Hochstetter have produced figures in evidence of the effects exerted by diverse conditions, such as the composition of the water, presence of other microbes, dissolved substances, and the action of carbonic acid, as, for example, in seltzer water. In this connection it should be remarked that carbonic acid under pressure confers no germicidal property upon seltzer water. Although the non-sporulating anthrax bacillus dies in it within an hour, the typhoid bacillus resists for from five days to twelve days, that is, about the same as in ordinary water.

The conclusion is that water furnished for drinking purposes always contains microbes.

Transmission of Infections by the Soil. The soil receives as many microbes as does water. These sink deep into the soil, but no further than three and one-half to four yards below the surface. At this depth the soil becomes sterile. The maximum is found at twenty inches (C. Fraenkel). Those remaining upon the surface are rapidly destroyed by the sun's rays. However, a little soil or dust

taken at the surface of the road almost constantly shows some pathogenic agents: pyogenic cocci, the bacillus of gaseous gangrene, of tetanus, and in certain localities the bacillus anthracis. Clinical studies supplementing the data of bacteriological research have established the telluric origin of the agents of dysentery, cholera, typhoid fever, tuberculosis, and icterus gravis. These various agents, as above stated, are found in and not upon the surface of the soil. They are brought to the surface on various occasions when, for instance, the soil or streets are dug or torn up for diverse purposes. Such work is too often followed by the outbreak of epidemics of typhoid fever, diarrhea, or icterus gravis.

Role of the Invertebrates in the Transmission of Infections. It has long been known that certain pastures were particularly dangerous as centres of anthrax infection. In Beauce such pastures were called "cursed fields." At times the focus was confined to a farm or a stable. Pasteur undertook the study of this mysterious question and discovered anthrax spores in the infecting soil in the neighborhood where anthrax animals had been buried several years before. Pasteur asserted that earthworms ingested the spores with the contaminated soil and, coming to the surface, deposited them with their excreta. Koch vigorously opposed Pasteur's theory. He argued that the soil is too cold to permit the vegetation and particularly the sporulation of anthrax. The soil, however, seems to be a good culture medium. Soyka[1] proved by experiment that the introduction of particles of quartz into liquids in which bacteria are cultivated markedly favors sporulation. It is further to be remarked that the temperature of the soil is higher around buried cadavers because of the heat generated by putrefaction.

Earthworms are not the only animals capable of conveying anthrax. The highly interesting experiments of Karlinski[2] demonstrate that snails may play the same rôle. Living spores were found in their intestines eleven days after ingestion of food containing anthrax bacilli. Insects, particularly flies, are often the agents of microbic transmission. At times they simply transport the germs from one point to another. At other times they inoculate them into healthy individuals. The typhoid bacillus passes through the intestine of the fly without perishing. Flies may also disseminate the tubercle

[1] Soyka. Bodenfeuchtigkeit und Milzbrandbacillus. Fortschritte d. Med., 1886.

[2] Karlinski. Zur Kenntniss der Verbreitungswege des Milzbrandes. Centralbl. f. Bakt., 1889, Bd. v.

bacillus, as has been proved by Spillmann, Haushalter, Hoffmann, and Moeller. As, however, the common fly is incapable of biting man, it simply diffuses the virus.

The rôle of mosquitoes is much more important. As early as 1848 Nott believed they conveyed yellow fever. In 1898 Grassi established the law of coincidence of malaria and certain mosquitoes—the *Anopheles* and especially *Anopheles claviger*. The bite of *Culex pipiens* is less dangerous, though not completely harmless (Laveran, Bignami, Bastianelli, etc.). It is also known that the African cattle disease caused by the tsetse fly is not due to venom, as was once supposed, but to inoculation of a parasite, *trypanosoma Evansi*. Bed-bugs may transport tuberculosis (Dewevre) and recurrent fever (Tiktine), while spirilla die inside these animals in forty-eight hours. The majority of other microbes perish very rapidly, so that, according to Nuttal's experiments, bed-bugs do not seem to be capable of propagating anthrax or bubonic plague. Ogata has shown that fleas found upon rats suffering from plague often contain the pathogenic bacillus. The flea of the rat is not, however, identical with that of man, and seems to be incapable of biting him.

All these extremely interesting facts tend further to reduce the rôle of the air and to establish the conclusion that infections are most frequently propagated by contact.

Role of Objects, Clothing, and Draperies. As early as 1868 Villemin rightly declared that "residences are foci of infection for man, and should be disinfected as is a stable contaminated by glanders." The floors, rugs, draperies, all furniture, and particularly clothing, may receive and carry infectious germs. Numerous instances demonstrate that clothing may cause the reappearance of an infection several years after exposure. Such, for example, was the case with the clothing of a child, the victim of diphtheria, which had been placed in a drawer and thus protected against the action of light. A year or two later, when taken out, they gave rise to fresh cases of diphtheria. Hence the necessity for vigorous disinfection of apartments, bedding, clothing, and vehicles of transportation which have served for the conveyance of a sufferer from some infectious disease.

Role of Plants. Infections may also be due to contamination by plants carrying pathogenic agents. This is particularly the case in aspergillosis and actinomycosis. The former disease attacks those who rear pigeons, not because the birds are diseased, but because

the individuals who feed them put into their own mouths grain contaminated with aspergillus fumigatus. Actinomycosis is very rarely contracted from men or animals. Man and the bovidæ are almost always infected through the agency of contaminated ears of corn or grain when the latter are chewed or the subjects are pricked by them.

Role of Aliments. Infections may be transmitted through ingestion of meat, viscera, and milk of diseased animals.

Some authorities claim that the flesh of animals suffering from anthrax may be consumed with impunity. According to Johne, the meat contains no spores. This assertion is contradicted by the experiments of Schmidt-Muhlheim. This scientist showed that Johne had examined only the interior of the meat, and that sporulation is possible upon the surface in contact with air. Such flesh should be proscribed, if for no other reason than to avoid the danger to which those who handle it are exposed. In the German statistics for 1887 it is found that anthrax developed twelve times through the use of contaminated meat. According to Puech, salting may destroy virulence. The experiments of Foster and Freytag contradict this conclusion. By growing anthrax in agar-agar containing an excess of salt these authors discovered that, while the bacilli died in twenty-four hours, the spores survived for several months. It must be remembered that the milk of animals infected with anthrax may contain virulent bacteria, as has been established by the researches of Chambrelent, Moussous, and Karlinski.

As regards the flesh of tuberculous animals, the Congress of 1888 demanded the total proscription of such meat. It is as yet difficult to express a final opinion in this respect. A certain number of contradictory experiments have been reported. Cooking and the action of the gastric juice do not suffice to destroy the tubercle bacillus. Finally, although the microbe is not present in the muscles it is met with in the glands, and this, perhaps, is a sufficient reason for prohibiting the consumption of such meat.

Role of Milk. Since Gerlach recognized that the milk of diseased cows may transmit tuberculosis, numerous experiments have confirmed his view and demonstrated the rôle of this fluid in the etiology of abdominal tuberculosis in children (Klebs, Orth, Cohnheim). From a hygienic standpoint, Gerhardt published an extremely interesting work upon this subject. Milk purchased in ten different places in Munich did not transmit tuberculosis. On the other hand, the milk

of consumptive cows always proved virulent. When this milk was diluted with forty to one-hundred volumes of non-infected milk, however, it was rendered harmless. This is just what occurs in dairies. The researches of Bang demonstrated the presence of virulent bacilli in butter. Heating of milk is, therefore, absolutely necessary. In this connection it should be remembered that a temperature of 65° C. (149° F.), and even 70° C. (158° F.), is not always sufficient to destroy pathogenic germs. Ingestion of milk thus treated has resulted in the transmission of the disease to swine, while rabbits, which are less sensitive to this mode of infection, usually resisted infection (Bang).

Since the milk of tuberculous cows so often proves to be virulent, we may justly assume that the milk of consumptive women is also a source of danger to their offspring. Here, perhaps, is a cause of infantile tuberculosis. We say "perhaps" for the reason that the results of experimental researches have thus far been negative. Escherich examined the milk of women suffering from pulmonary tuberculosis, but he was unable to discover any bacilli. It seems, however, that he did not make inoculation experiments. In 1892 Fede studied the question more thoroughly.[1] He injected the milk of tuberculous women into the subcutaneous cellular tissue, peritoneum, and anterior chamber of the eyes of rabbits and guinea-pigs, and never observed the development of tuberculosis. These results were confirmed by Bonis. The experimental inoculations of Bang were likewise negative. The author observed a case which contradicted the classical opinion and showed that the milk of a consumptive may possibly prove virulent.[2]

The case in question was that of a woman, thirty-four years of age, who entered the hospital February 16, 1896, for a pharyngeal tuberculosis. She was pregnant, and confinement occurred under favorable conditions. From that moment the symptoms became aggravated, and the woman died on the 24th of March, seventeen days after childbirth. The necropsy showed advanced tuberculous lesions in the lungs and gray granulations in the liver, kidneys, and thyroid gland.

Two days after birth the child became jaundiced, and then green

[1] W. Fede. Transmissibilita della tuberculosi per lattazione. Congresso pediatrico italiano. (Anal. in Riforma la Medica, 1892, vol. iv. p. 236.)

[2] Roger et Garnier. Passage du bacille de Koch dans le lait d'une femme tuberculeuse. Soc. de biol., Feb. 24, 1900.

diarrhea and edema of the lower extremities supervened. The infant was first fed from the bottle, but the mother undertook to nurse it when she observed that it was ill. She gave it her milk from the 10th to the 12th of March. Aggravation of her condition, however, prevented her from further suckling her offspring. The child lived six weeks. At the necropsy numerous tubercles were discovered in the liver, spleen, kidneys, and mesenteric glands. On histological examination of the liver typical tuberculous granulations containing Koch's bacilli were found.

On March 11th, four days after confinement, two guinea-pigs were inoculated with milk taken aseptically from the mother's breast. One guinea-pig, weighing 440 grams, received 4 c.cm. of the milk subcutaneously; 2 c.cm. only were injected into the peritoneal cavity of the second guinea-pig, which weighed 525 grams. The former animal died much emaciated on the 14th day of April, and at the necropsy presented typical lesions of generalized tuberculosis. The other animal survived. It weighed 565 grams on April 21st, and 650 grams on June 14th. It presented hypertrophied glands in the groin, however. It was killed on the 28th of the following January. At the necropsy a fibrous peritonitis was found at the point of inoculation. The intestinal coils were adherent to each other and to the lateral wall of the abdomen. The omentum was thickened and contracted, free from visible tubercles. The rest of the abdomen presented no lesions. The surface of the liver was studded with depressed points resembling cicatrices. Microscopic examination of the viscera showed no tuberculous granulations, sclerotic lesions, or bacilli.

Of the two guinea-pigs, therefore, only one became tuberculous. The one which received the larger dose of the milk developed tuberculosis according to the usual mode, and death occurred in thirty-three days. The other animal, which received half the amount of milk injected into the former animal, survived and seemed to be in excellent health when it was killed, ten months after inoculation. It had not, however, remained absolutely immune. The injected milk had not acted as an indifferent liquid, since a fibrous peritonitis developed at the point of inoculation, and thus manifested the pathological process that had taken place there. Moreover, a hypertrophied gland in the groin and traces of cicatrices upon the surface of the liver proved that generalization had begun. The history of the first guinea-pig enables us to explain the lesions present in the second

animal. In the former the quantity of injected bacilli was large enough to overcome the resistance of the organism, and tuberculosis was generalized. In the case of the second guinea-pig, the dose being smaller, infection was abruptly arrested: the lesions were repaired and common cicatrices only, without any characteristic elements, were found.

It must be concluded that the injected milk contained bacilli, and was, therefore, capable of transmitting tuberculosis. It is true the child was exposed to sources of contamination other than that of suckling. However, as the necropsy upon the child showed that the lesions predominated in the mesenteric glands, liver, and spleen, it is probable that the digestive canal was the principal if not the only route of contamination.

Therefore, the milk of a tuberculous woman may, in exceptional instances, serve as a vehicle for Koch's bacillus even in the absence of appreciable tuberculous lesions in the mammary glands.

In the course of acute infectious diseases the milk of women seems to be free of virulence. The unfavorable results of artificial feeding, especially among the poorer classes, led me to allow sick mothers to nurse their children. The first attempts were made in cases of erysipelas, the writer having previously learned that the milk contained no streptococci. Nine children were suckled by the mothers, three others were allowed mixed alimentation in order to compensate for the diminished amount of mother's milk. Under these conditions all the children thrived.

Suckling was likewise continued in other diseases. Over one hundred women suffering from measles, scarlatina, mumps, or sore throat nursed their infants. Among these, two only contracted measles, and then only in a very mild form. This immunity of infants leads one to believe that the milk contains immunizing substances from the very beginning of the mother's illness. Whatever the correct interpretation of the fact may be, the innocuousness of suckling seems to be well established.

Autoinfections.

The reality of morbid spontaneousness is recognized and proclaimed by clinicians as is that of contagion. In fact, infectious diseases are seen to develop without any accidental contamination. They occur under conditions which preclude the intervention of external

germs. When an individual has an attack of pneumonia as the result of exposure to cold, we at times search in vain for some external origin of infection. The same is true of cases of sore throat, erysipelas, osteomyelitis, and typhoid fever, in which the minutest inquiry and the most attentive examination fail to reveal a focus of contamination. Therefore, a functional disturbance is supposed to have been produced by some ordinary cause.

A diametrically contrary view arose when the advances of bacteriology revealed the animate agents of infections. Contamination by a certain microbe was assumed to be necessary for the development of every case of infection of a definite character. This simple theory was not in harmony with clinical observation. The enthusiasm aroused by new discoveries was so intense, however, that the unexplained facts of clinical observation were unhesitatingly denied.

Finally, science has succeeded in harmonizing the contradictory and exclusive theories. Morbid spontaneousness is again admitted. It rests, however, upon a new basis. An infectious disease often appears to be due to a series of microbes which constantly reside upon our mucous membranes and epidermis. Under normal conditions the organism either does not permit these dangerous guests to penetrate into its interior, or it rapidly destroys those which pass the epithelial barriers. When, however, the organism is disturbed by some influence, the microbes invade it. Infection is then justly said to have been spontaneous—*i. e.*, to have developed without any outward contamination.

Distribution of Microbes within the Normal Organism. It is readily understood that microbes, being abundantly distributed around us, must necessarily be encountered on every part of our organism in contact with the external world.

At each inspiration a certain number of bacteria are carried with the air into the respiratory passages. They are, however, arrested in their course by various organs: by the hair in the nasal cavities, by the vibrotile cilia of the bronchial mucous membrane, and by the secretions, so that the air is often bacteriologically pure in the pulmonary alveoli and even in the bronchioles. In sweeping back through the respiratory tract the air does not take up any germs once deposited, since, as has already been stated, microbes can never leave liquid media. The expired air, therefore, contains no bacteria.

The respiratory apparatus is happily provided with various means of protection against microbes. The secretions act mechanically,

and, so to speak, wash the mucous membrane. A certain number of bacteria are thus thrown out, others are destroyed by the nasal mucus, which possesses, as Lermoyez and Wurtz have shown, a germicidal power, viz., exert a sort of antiseptic action. The remainder is incorporated and devoured by phagocytes which greatly abound in the pulmonary alveoli and wherever lymphoid tissue is highly developed.

Bacteria are found in far larger numbers in the alimentary canal. The buccal cavity contains the most varied species, among which some endowed with pathogenic properties are almost constantly present. Such are the pneumococcus, the streptococcus, and the micrococcus tetragenus. The gastric juice has not such germicidal power as was formerly believed, since recent enumerations demonstrate that this portion of the alimentary tract contains large numbers of bacteria, even more than the duodenum.

The microbes find in the intestines conditions most favorable to their existence. They are in nowise disturbed by the secretions elaborated there, and they find an abundant supply of food. It may, therefore, be said that the intestine is the paradise of microbes. The following figures, borrowed from the interesting contributions of Gilbert and Dominici, show how well they thrive there: 50,000 microbes per cubic millimetre are found in the stomach. In the first part of the duodenum the number is only 30,000 per cubic millimetre. From this point the number progressively increases until the lower portion of the intestine is reached, where the maximum number, 100,000 per cubic millimetre, is found. In the cecum another fall occurs, and throughout the large intestine the number is 25,000 to 30,000 per cubic millimetre. When the quantity of fecal matter contained in the alimentary canal is taken into account, the remarkable total of 411,000,000,000 of microbes is reached.

The digestive tract is protected against microbes in the same manner as in other parts of the organism. The intestinal and pancreatic juices and the bile, though possessing no germicidal power, serve to sweep away and expel both microbes and their toxins. Those micro-organisms which pass through the mucous membrane are arrested by the lymphoid structures, follicles, and glands of Peyer, and by the numerous leucocytes which are constantly wandering in this region and may even enter the cavity of the intestine. Should any microbes escape these agents of destruction they are arrested in the lymphatic glands and in the liver, where new defensive

measures are united. Should they pass further, they reach the lungs, which are likewise endowed with germicidal power. We thus see how numerous are the defenses provided to antagonize the intestinal microbes, since the danger of invasion of the economy by resident microbes is found especially in the alimentary canal.

The genito-urinary organs also contain bacteria, at least in their external portions. The researches of Stroganoff, Menge, and Kroenig have shown that the vaginal secretion is richly endowed with germicidal properties. If some inoffensive bacterium, such as the bacillus pyocyaneus, or a pathogenic micro-organism, such as the streptococcus or the staphylococcus aureus, is deposited deep within the vagina they are soon destroyed.

With regard to the urinary passages, it is admitted that bacteria do not ascend the urethra and never penetrate the bladder, and since the time of Pasteur it has repeatedly been stated that urine voided aseptically does not decompose. Recent researches, however, tend to demonstrate that such is not always the case. The investigations of Lustgarten, confirmed by those of Dr. Courtois in our laboratory, show that the urine of healthy individuals frequently contains micro-organisms. Lustgarten describes eleven species, one of them very peculiar, namely, the streptococcus giganteus urethræ, the chains of which are composed of several hundreds and even more than a thousand individual cocci. The length of the chain is equal to five or six times the diameter of the field of the microscope. This streptococcus is not pathogenic for rabbits. Five cubic centimetres of a bouillon culture was injected into the veins, and in order to render its action more efficacious we at the same time introduced 1 c.cm. of a sterilized culture of bacillus prodigiosus. The result was negative, since the animal manifested no disturbance.

Autogenic Infections. Of the microbes which are found in living organisms under normal conditions, some always remain harmless; others become pathogenic as soon as some unfavorable occurrence weakens the resistance of the economy. They can then penetrate the barriers and give rise to various lesions. Upon the skin acne, furuncles, anthrax, and at times gangrene or erysipelas appear. In the buccopharyngeal cavity: anginas and phlegmons of the tonsils, in the respiratory apparatus: bronchites, bronchopneumonias, and fibrinous pneumonia; in the intestines: diarrhea, either simple, choleriform, or dysenteriform, etc., occur. The microbes may also secondarily or primarily invade the organism at large and produce

septicemia or pyemia, and thus give rise to numerous visceral lesions.

In this connection, typhoid fever requires special consideration. As soon as an epidemic of this disease breaks out, the drinking water is subjected to minute examination, and if a bacillus more or less analogous to that of Eberth is encountered, the entire etiological problem is believed to be solved. We are told that improved canalization and pure water supply are the best means to overcome a typhoid epidemic, and, in many instances, practice has amply justified this theory.

Some epidemiologists, however, refuse to accept a theory so exclusive. The penetration of the bacillus into the organism does not seem to them sufficient to elucidate the etiology of typhoid fever. Army physicians, who are usually in a position to follow the course of epidemics, constantly protest against the exaggerations of some authorities.

Dr. Arnold in an article in the *Dictionnaire encyclopédique*, and Dr. Kelsch,[1] in his treatise on epidemiology, seem to have gone to the root of the question.

In view of the great readiness with which typhoid fever makes its appearance as a result of overwork, and especially under conditions of overcrowding, such as exists in the case of armies in camp, it may well be questioned whether man does not carry within himself the germ of the disease, and whether external contamination is really necessary.

Kelsch[2] fully demonstrates that the rôle of overfatigue and of crowding are potent etiological factors. These bring in their train contamination of the soil and water. Typhoid fever, therefore, invariably appears in camps, and particularly in permanent camps, at the end of five or six weeks, when the men are exhausted by overwork. It may be objected, however, that some of the men were sick when they left the city, or that the disease was in the stage of incubation. It is necessary, however, to pile up a good deal of the most hypothetical reasoning in order to support the dogma of morbid specificity. The etiology becomes singularly simplified and rational when the malady is attributed to endogenic origin, that is to autoinfection, or, in other words, when it is assumed that men carry the germs of the malady in the form of saprophytes, and that overwork,

[1] Kelsch. Traité des maladies épidémiques, Paris, 1894. [2] Ibid.

by diminishing their vital existence, permits the transformation of these saprophytes into pathogenic agents.

Admitting, however, that an animate agent is indispensable for the production of an infectious disease, and that there are two orders of microbes—specific and non-specific—the question arises: to which order does the microbe of typhoid fever—Eberth's bacillus—belong?

Most bacteriologists answer that it belongs to the specific order. Drs. Rodet and Roux have advanced a contrary opinion. According to them the typhoid bacillus is but a variety of colon bacillus. As is known, this theory provoked a great deal of controversy. In fact, confidence was gradually lessened as to the destructive character of Eberth's bacillus, as the latter was proved to have no absolute value. Most recent researches, however, have furnished a new method for recognizing the typhoid bacillus. The serum of an animal that has been vaccinated against a duly verified specimen of this microbe is employed and its agglutinating action noted upon the bacillus which is to be identified. By the employment of this method, which seems to be unassailable, Drs. Remlinger and Schneider[1] demonstrated the presence of the typhoid bacillus in water obtained far from epidemic foci, in the soil, and, what is of far greater consequence, in the alimentary canal of individuals free from typhoid fever. The last fact is, as has been said, of considerable interest, since it explains previously obscure facts and harmonizes bacteriology and epidemiology. Dr. Kelsch is, therefore, right in stating, according to the data of clinical observation, that typhoid fever may be produced by germs carried in our bodies and which, although harmless saprophytes under ordinary conditions, temporarily manifest virulent functions under the influence of marked violations of hygiene, notably prolonged fatigue, defective regimen, ordinary pollution of water—all circumstances which, by virtue of their combination, are so powerful in creating a putrid state in the internal medium.[2]

Such is the rational conception which we may at present form with regard to the etiology of typhoid fever. It is the view which I have advocated, in a study made some years ago.[3] These ideas, which were described in detail by Dr. Bourgeois,[4] aroused bitter criticism.

[1] Remlinger et Schneider. Contribution a l'étude du bacille typhique. Ann. de l'Institut Pasteur, January, 1897.

[2] Kelsch. Loc. cit., p. 453.

[3] Roger. Etiologie et pathogénie de la fièvre typhoïde. Presse médicale, March 17, 1894.

[4] Bourgeois. Etiologie et pathogénie de la fièvre typhoïde. Thèse de Paris, 1894.

The discovery of Drs. Remlinger and Schneider demonstrates beyond all doubt the truth of the view to which I was led by an impartial study of typhoid epidemics.

The Autogenous Origin of Various Specific Infections. Among other diseases which, perhaps, at times appear spontaneously, diphtheria should first be mentioned. Bacteriology has already established the presence in the mouth of a bacillus analogous to that discovered by Loeffler. Does this non-virulent pseudodiphtheria bacillus represent an attenuated variety or a distinct species? This is an important and as yet unsolved problem. Likewise the spontaneous origin of gonorrhea cannot be admitted except with the greatest reservation, viz., its appearance in the absence of sexual intercourse, as in the well-known observation of Straus.

It may be asked whether the germs of the eruptive fevers are not often present in the bodies of healthy individuals. My personal statistics, covering 304 cases of measles, 340 of scarlatina, 69 of varicella, and 38 of variola, show that in a great number of cases the minutest inquiry fails to reveal any mode of contamination. We merely present the question of the autogenous origin of these various affections. A decision must be reached through bacteriological investigation. In the case of eruptive fevers it may be assumed that the mode of contamination is so often undiscoverable because their germs are perhaps widely distributed and because some of these fevers, particularly measles, are contagious in the prodromic stage, previous to all serious manifestations, when contact is scarcely noticed.

Auxiliary Causes of Infections.

Meteorological and Seasonal Influences. The rôle of cosmic influences has at all times been accepted. This is evidently due to the fact, which is open to popular observation, that the frequency of infections is subject to quite regular oscillations each year. The accompanying table gives a résumé of my personal statistics, and shows plainly that, each year, infectious morbidity runs nearly a parallel course. The minimum is observed in October and November. Then follows an increase which reaches the maximum in the spring, from April to June or July. The figures of each year are almost the same. It is to be noted that measles appears earlier in the year than scarlatina, and reaches the highest point in April and May. On the other hand, scarlatina increases until June. Although

less pronounced, variations of anginas of diphtheritic or other type are, nevertheless, clear.

	1896	1897	1898	1899	1900	Total.
Measles.						
Number of cases observed	304	379	398	366	370	1817
Cases with contagion	79	83	74	89	63	388
Percentage	25.1	21.8	18.5	24	17	21.3
Percentage in men	19.5	18.3	10.8	21	13	17.6
" women	30.4	21.6	29.6	24	17.6	26.2
" the newborn	31.9	27.9	20	25.7	25	26.8
Scarlatina.						
Number of cases observed	340	161	496	779	437	2213
Cases with contagion	53	18	75	174	53	373
Percentage	15.5	11.1	15.1	22.3	12 1	16 8
Percentage in men	8.6	6.2	9.7	16	12.6	12.5
" women	21.1	14.4	19	25	13.8	20.1
Varicella.						
Number of cases	69	52	45	32	117	315
Cases with contagion	23	14	9	1	44	91
Percentage	33.3	26.9	20	3.1	37.6	28.8
Variola.						
Number of cases	38	20	2	1	928	989
Cases with contagion	14	8	1	1	246	270
Percentage	36.8	40	50	100	26.5	27.3

The greatest number of cases of this kind are observed in May and June. It is to be noted also that mumps is particularly prevalent in April and May, and seldom occurs during the months of October and November.

In this connection smallpox is a remarkable exception. The cases occur with nearly the same frequency throughout the year.

In the author's table the figures for erysipelas are those of the year 1900 only. The variations here shown, however, are entirely comparable to those occurring in the eruptive fevers.

The influence of seasons is doubtless ascribable to manifold causes: thermometric, barometric, and hygrometric variations, the action of the sun, rain, wind, and thunder-storms, and the rôle of ozone are causes readily perceived. Do these influences, however, affect the morbid germs or the higher organisms? Both hypotheses have equally competent defenders. It seems that the lower the animal organism, the better it resists cosmic variations. Variations in pressure and temperature which would rapidly kill a mammalian act indifferently upon bacteria. It is more likely, therefore, that the receptivity of the human organism is modified by disturbing meteoric causes. It is difficult, however, to further elucidate this rather vague problem. All that can be added is the fact that respiratory disturb-

ances are especially frequent when variations of temperature occur and, principally, in the spring. Thoracic complications in the course of infections such as erysipelas and variola are almost always observed during the period from the month of March to the month of May. On the other hand, heat favors the genesis of gastrointestinal affections.

After the monthly variations, those embracing longer periods must be considered. Variations in the cases of smallpox may be due to negligence in the matter of vaccination. It is difficult, however, to account for the changes occurring in a disease like scarlet fever. A tabulation of our cases from 1896 to 1900 shows the number of cases increasing progressively from 161 to 496, reaching a maximum of 779, and then suddenly declining to 437. It is curious to note that the variations in anginas correspond exactly to those occurring in scarlatina. The eminent rôle of sore throat in the symptomatology of scarlatina lends a certain interest to this parallelism. Measles, on the contrary, presents almost no variation. On an average, we receive from 360 to 380 cases annually. As in the case of frequency, the gravity of cases undergoes periodical variations. The history of scarlatinal epidemics observed in England and of epidemics studied by Bretonneau in Tours clearly demonstrates this.

The influence exerted by climate is still more marked than in the case of seasons. There are countries in which certain infectious diseases cannot become acclimated. Yellow fever, which claims so many victims in certain portions of the new world, seldom appears on the old continent.

In this respect the sanitary conditions of a country are of the greatest importance. The number of infectious cases has considerably diminished since the advance of disinfection, the creation of special hospitals for the isolation of contagious cases, and the improvement of drinking water. Even typhoid fever is at present less frequent.

Influence of Race and of Family. Morbid receptivity varies considerably in different races. The negroes are immune from certain infections, such as yellow fever, and very seldom suffer from malaria. On the other hand, they are very susceptible to tetanus.

The yellow race is predisposed to variola, which prevails in China in an endemic form.

Acute articular rheumatism is confined almost exclusively to the Caucasian race.

If we pass from race to family we encounter analogous facts. There are families particularly sensitive to tuberculosis, or diphtheria, or erysipelas. From this point of view I have questioned 956 men and 1044 women suffering from erysipelas. Many of them were incapable of giving any information. Taking into account, however, the accurate replies, I find that erysipelas existed in the families of 94 men and 110 women, which gives a ratio of 9.8 per 100 for the former and 10.5 for the latter. Simple coincidence does not adequately account for so high a proportion. Moreover, our figures are below the actual number, as many patients were unable to state whether their parents had ever had an attack of erysipelas. The following table gives the family history of this affection and shows that, in many instances, the parents had several attacks and the malady ran through several generations:

	Parents having erysipelas:	
	Once	*Several times.*
Father	21	8
Mother	54	37
Father and mother	2	3
Grandmother	7	11
Grandmother and father	7	2
Grandmother and mother	7	3
Brother or sister	22	17
Father and brother	22	1
Mother and sister	3	1
Uncle and aunt	4	5
Children	3	5
	152	93

In the majority of cases contagion is not to be thought of, for the children were either far removed from the parents or erysipelas appeared after the death of the latter. One of the most curious observations in this respect is that of a man, fifty-five years of age, whose mother had experienced twelve attacks of erysipelas. He, himself, was suffering from his fourteenth attack. While he was under treatment in our wards, his son, who was enlisted in a regiment of dragoons in Sedan and had not seen his father for over six months, had his first attack of facial erysipelas. On other occasions I observed two sisters who, although not residing together, synchronously contracted facial erysipelas, and, what was more curious, the affection assumed a wandering course in both, and invaded the greater part of the trunk.

It seems that the streptococcus, like many other microbes, finds in certain families a soil particularly favorable for its development.

Individual Immunity and Predisposition. There are numerous individual variations; some persons have often exposed themselves to contagion, even to vaccination, without being contaminated. A great number of cases have been reported in which vaccination has not taken. The same thing is at times observed in laboratories. One animal resists, while others, apparently similar, placed under identical conditions and inoculated in the same manner, die without exception.

In some cases, insensible gradual vaccination may account for individual immunity. The natives of Paris, for instance, do not, as a rule, contract typhoid fever, which does not spare all individuals arriving from the country. The reason is that Parisians from their infancy have been little by little impregnated with the germ. Thus becoming gradually habituated, they have either suffered no disturbance or manifested symptoms too mild and vaguely characterized to be traced to their true course.

Insensible vaccination also explains the disappearance of epidemics. If, at a given time, the cases diminish in number and severity, this is due to the fact that the population has slowly been subjected to insensible vaccination. The immunity of physicians is due to no other cause.

The fact that an infection loses its gravity in the course of centuries, or acquires unusual malignancy when it invades a people until then immune, may be attributed to an analogous process. The epidemics of measles in the Faroe Islands clearly illustrate this fact. The disease was imported into these islands in 1846. Of the 7782 inhabitants, 6000 were attacked, the aged alone being spared. In 1875 the same malady invaded the Fiji Islands and killed 40,000 persons out of a population of 150,000.

Influence of Age, Sex, and Accidental Disturbances. Morbid aptitude varies considerably with age. During intrauterine life the fetus is exposed to some diseases the germs of which are transmitted through the placenta. At the time of birth the individual offers sufficient resistance to the majority of infections; vaccination does not take, eruptive fevers, as well as typhoid fever and diphtheria, are altogether exceptional. On the other hand, erysipelas, which is generally localized in the navel and almost invariably proves fatal, is very readily contracted by the newborn.

Infectious diseases are frequent during childhood. At this epoch of life the tissues are particularly apt to permit the development of

parasites. Pityriasis, for instance, does not thrive in the aged, and spontaneously disappears with the advance of years.

The frequency of infections diminishes with age. In the aged scarcely any other disorders than vesical infections and pneumonia occur. Does the immunity of old age depend upon previous diseases and insensible vaccination? Not altogether. A certain influence must be attributed to the modifications produced in the chemical constitution of the tissues and humors. This is proved by the fact that when measles invaded the Faroe Islands only the aged were spared by the disease, which was unknown up to that time.

The influence of sex is no less interesting. It seems that women are predisposed to the infections of childhood for a longer period than men. The eruptive fevers, which are quite rare among men after the age of twenty years, are frequently observed among women between twenty-five and thirty years of age.

The following table presents the results of my personal observations from this point of view:

MEASLES.

	Men.	*Women.*	*Total.*
Before 2 years	160	194	354
2 to 14 years	119	122	241
15 to 20 "	300	224	524
21 to 25 "	128	247	375
26 to 30 "	82	120	202
31 to 35 "	38	42	80
36 to 40 "	13	16	29
41 to 45 "	4	5	9
46 to 50 "	1	1	2
51 to 60 "	1	..	1
Total	846	971	1817
Adults above 15 years	567	655	1222

SCARLATINA.

	Men.	*Women.*	*Total.*
Before 2 years	29	27	56
2 to 14 years	228	202	430
15 to 20 "	388	369	757
21 to 25 "	167	338	505
26 to 30 "	85	167	252
31 to 35 "	44	82	126
36 to 40 "	19	29	48
41 to 45 "	9	8	17
46 to 50 "	4	8	12
51 to 60 "	2	8	10
Total	975	1238	2213
Adults above 15 years	718	1009	1727

VARICELLA.

	Men.	*Women.*	*Total.*
Before 2 years	57	46	103
2 to 14 years	69	54	123
15 to 20 "	18	16	34
21 to 25 "	17	10	27
26 to 30 "	8	6	14
31 to 35 "	4	3	7
36 to 40 "	2	2	4
41 to 45 "	..	2	2
46 to 50 "	1	..	1
Total	176	139	315
Adults above 15 years	50	39	89

VARIOLA.

	Men.	*Women.*	*Total.*
Before 2 years	20	12	32
2 to 14 years	40	22	62
15 to 20 "	88	59	147
21 to 25 "	80	105	185
26 to 30 "	50	105	155
31 to 35 "	56	71	127
36 to 40 "	45	55	100
41 to 45 "	27	28	55
46 to 50 "	22	24	46
51 to 60 "	20	29	49
61 to 91 ',	16	15	31
Total	464	525	989
Adults above 15 years	404	491	895

These figures show the influence of sex and age upon the frequency of the eruptive fevers. From fifteen to twenty years of age measles and scarlatina are more frequent among men than women. At twenty they undergo a sudden fall in the male sex, while among women they remain at a very high level.

The study of variola shows plainly the beneficial influence of vaccination. Children are not frequently attacked. The disease increases after the age of fifteen years. The maximum for men is reached from fifteen to twenty years of age. Among women the frequency increases, exceeds that of the other sex, and remains high from twenty-one to thirty years of age.

The variations according to sex are less marked for the other infections. Thus, the author found that 134 men and 122 women were attacked by diphtheria, and 385 men and 407 women by anginas. According to the author's statistics, mumps seems to be more frequent among men than women, as he has found 170 of the former and only 65 of the latter affected with this disease. This result is probably due to the greater gravity of the disease in men

and to the frequency of orchitis which compels them to enter the hospital.

The different acts of genital life invest feminine pathology with a peculiar character. Menstruation may be an occasional cause of infectious manifestations. Such, especially, is the case in erysipelas, an attack of which may attend each period. Certain women thus experience fifty and sixty relapses.

Pregnancy may modify the course of certain infections. Not infrequently tuberculosis seems to be arrested and, after confinement, the disease assumes a more rapid course. It is hardly necessary to refer to the frequency of puerperal infections. In this case, however, the diseases present nothing special. The puerperal woman is in the same situation as a wounded one.

All violations of the laws of hygiene predispose to infections. The noxious effects of overcrowding have already been referred to. The influence of previous diseases is well known. Some of them predispose to infections. Diabetes favors the development of pyogenic microbes and of the tubercle bacillus. Pneumonia, erysipelas, and rheumatism, far from conferring immunity, predispose to new attacks. As a rule, however, infections create a refractory state and prevent future attacks. It is well to add, however, that immunity is in no case absolute except, possibly, in syphilis.

Among causes which lessen individual resistance, the influence of external agents is of chief importance. Serious traumatism, crushings, and extensive contusions diminish considerably the resistance to invasion by microbes.

The action of cold and heat is very complex, for they do not act simply by modifying the temperature of the body. The fact that chickens, which are naturally immune to anthrax, contract this infection when they are exposed to cold, and that, on the contrary, frogs lose their immunity when exposed to high temperatures, is not due to modifications of the organic temperature thus produced in these animals. In reality the phenomena are more complex. When chickens are exposed to cold and frogs to heat, nutrition is disturbed; the life of the cells, and consequently the constitution of the humors, is altered; the heart, the nervous system, and the leucocytes are acted upon. Abolition of immunity is, therefore, the result of manifold factors.

Action of Poisons upon Infections. A great number of poisons diminish the resistance of the organism to infectious agents.

Seeck noticed that various parasites developed upon the skin of frogs treated with metallic poisons. Some of the lesions observed in the course of intoxications are in reality due to secondary infection. Such is the case in mercurial stomatitis or enteritis. The mercury during elimination by the mucous membranes denudes the latter of their epithelium and prevents them from resisting invasion by the numerous microbes swarming upon their surfaces. It is, therefore, conceivable that mercurial stomatitis may be contagious, as in an observation of Diday, which illustrates in a striking manner the increased virulence which the buccal microbes may acquire in the course of intoxications.

Poisons favor infection in two principal ways: in some instances they produce local lesions which weaken the resistance of the tissues into which the poisons are introduced: in other cases they give rise to general disturbances of the economy, which abolish its immunity. As an example of the former mechanism, we may cite the action of lactic acid, which, when injected into the muscles of a rabbit, renders this animal incapable of resisting symptomatic anthrax. Other substances, such as acetic acid, potassium acetate, and alcohol, produce similar effects. Many antiseptic substances act in the same way. Hence, the increasing tendency to substitute asepsis for antisepsis in surgical practice or to utilize less energetic substances, such as boric acid.

In other instances the process is one of general intoxication, affecting probably the nervous system. Thus Platania demonstrated that alcohol and chloral favor the development of anthrax in naturally immune animals, such as the dog, the pigeon, and the frog. Wagner verified the fact by inoculating anthrax into chickens treated with chloral.

Influence of Autoinfections. A last group of poisons favoring invasion by bacteria is represented by substances which originate within the organism itself. Such occurs, for instance, in overworked animals: the toxins produced under these conditions favor the multiplication of attenuated viruses or the entrance of the numerous bacteria normally inhabiting the intestine. Diabetes and glycosuria likewise induce infection as a result of chemical modifications. This result, which has long been recognized by chemical observers, was experimentally verified by Bujwid, who injected sugar into inoculated animals, and by Leo, who administered to them phloridzin. In both instances infection was facilitated or rendered graver.

Certain organic lesions probably act by disturbing the chemical constitution of the organism. Neumann demonstrated that the development of the streptococcus may be favored by altering the function of the liver, by modifying the alkalinity of the blood, by producing lesions in the kidney, or by ligating the lower part of the intestine. In all these cases there is either excessive production of toxic substances or insufficient elimination.

Finally, microbes create morbid dispositions and favor the development of secondary infections through the toxic substances which they secrete. This fact will again be referred to when treating of morbid associations.

Influence of Fasting. This influence was known to the ancients, since epidemics following famines leave no doubt as to their connection as cause and effect. Likewise, the frequency of infections, from tuberculosis to gangrene, in patients who cannot be nourished, is a fact open to popular observation. The experiments of Canalis and Morpurgo demonstrated the rôle of starvation in this respect. The resistance of the organism is reduced not simply by suppression of alimentation, but also by insufficiency or bad quality of food. The influence of such conditions was well observed by clinicians, notably with reference to tuberculosis. The method of treatment by overfeeding consumptives is the opposite of the mentioned conditions. Analogous results are observed in experimental medicine. I have discovered that rabbits, when abundantly nourished, frequently resist inoculation of variola pus or culture, while similar animals receiving ordinary rations succumb to this affection. This observation led us to nourish patients suffering from smallpox, and with satisfactory results.

The results are altogether different when we operate upon animals which, after having been subjected to a sufficiently long period of starvation, have again been supplied with their ordinary food for several days.[1] Under these conditions the resistance is increased to a remarkable degree, at least with regard to the colon bacillus. It would not be correct to generalize the results which we have obtained with the latter microbe, which is the only one with which we have thus far experimented.

We starved five rabbits for five to seven days and then fed them. Three to eleven days later we made intravenous injections of *B. coli*

[1] Roger et Josué. Influence de l'inanition sur la résistance à l'infection colibacillaire. Soc. de biologie, July 7, 1900.

into them, as well as into control animals of equal or greater weight. At this time the animals which had been subjected to fasting had grown fat, but had not yet recovered their former weight. Of these five animals, only one died, five days after the inoculation. Of the five control animals, only one survived.

It may be asked whether fasting, as prescribed by certain religious rites, is not of greater hygienic importance than is believed, and whether the modifications produced by fasting do not finally strengthen the defensive means of the organism.

Influence of Fatigue and Overwork. The accidents following excessive fatigue have long held the attention of observers. Fatigue diminishes the resistance to microbic diseases. If it is not permissible to believe, as did the ancient veterinarians, that fatigue suffices of itself to create glanders and anthrax, it may be admitted that it favors or aggravates the development of these maladies. This is clearly seen from the interesting observations collected by Solowieff concerning both man and the horse. Clinical facts, however, are so very complex that it is impossible to define the rôle of fatigue. The infectious diseases developing in army camps are not altogether due to the excessive work imposed upon the soldiers. The emotions, the privations, the crowding, and other bad hygienic conditions must also be taken into account. We, therefore, thought it well to transfer the question to experimental ground, and with this end in view, we pursued a certain number of researches upon animals.[1]

We fatigued various animals—guinea-pigs, rabbits, white rats, cats, dogs—and determined the influence of overwork upon the results of inoculations. For this purpose we used the anthrax bacillus and the bacillus of symptomatic anthrax.

General fatigue induced in animals inoculated either with anthrax bacillus or the bacillus of symptomatic anthrax favors considerably the development and generalization of infections. The overworked animals invariably died before those left at rest. Quite often they succumbed while the latter resisted. It must be noted that animals of the same size and submitted to the same exercises by no means possess the same morbid aptitude. Some resist better than others, but these individual variations are observed in all experiments and in nowise modify the meaning of the results which we have obtained.

If general, fatigue explains the development of infections, the over-

[1] Charrin et Roger. Contribution a l'étude expérimentale du surmenage. Son influence sur l'infection. Arch. de physiol., Feb. 19, 1890.

work imposed upon an organ may account for certain clinical forms. Cerebral rheumatism, for instance, occurs only in individuals addicted to intellectual activity, or in those whose nervous system has suffered from late hours, dissipation, ambition, and disappointment. Likewise, in young subjects, growing bones are predisposed to microbic localizations, as expressed by the development of osteomyelitis. Conversely, an inactive organ does not offer a soil for the localization of microbes. Children suffering from mumps do not develop orchitis; this localization does not occur until after puberty.

Development of Epidemics; Their Variations with Countries and Epochs. The facts above reported lead to the conclusion that in all infections two factors are to be taken into consideration: (1) an external factor, the pathogenic microbe; (2) an internal factor, the state of the organism.

The pathogenic microbe comes from without. It was primarily a simple saprophyte, which accidentally settled in a living being, its special organization enabling it to accommodate itself to the new medium. It thus loses its ability to thrive outside living organisms, and acquires new qualities varying so greatly from the original that it is impossible to refer the isolated pathogenic microbe to the saprophytic species from which it evolved.

After the microbe has once acquired virulent properties it does not remain immutable. On the contrary, it is modified by various circumstances, its virulence increases or diminishes, and it acquires a special aptitude to vegetate in certain tissues rather than in others. The evolution of pathogenic microbes through the ages and countries thus leads us to admit that the clinical types also cannot remain immutable. It is conceivable that new infections may appear under the influence of cosmic and many other fortuitous agencies, and that affections of ancient origin may be modified or disappear.

In view of the fact that epidemics are at times suddenly revived and reigning infections assume unusual gravity or exceptional mildness, it must be admitted that infectious agents may become suddenly more or less virulent under the influence of changing atmospheric conditions. It is more likely, however, that the various cosmic changes act with greater energy upon the invaded organisms than upon the invaders. As has already been stated, the more highly developed and delicate the animal organization, the more sensitive it is to variations in the surrounding medium. For instance, man is influenced by changes in atmospheric pressure or thermal

variations, far more than the microbe. The explanation of "génie épidémique" must, therefore, be sought in the disturbances manifested in massed humanity. The appearance, course, more or less extensive ravages, and decline or disappearance of epidemics depend chiefly upon the influence exerted by meteoric, hygienic, and social conditions upon human organisms.

The insufficiency and laconicism of ancient descriptions make it difficult to compare the diseases of the present time with those of the past. With reference to some of them, however, the course of evolution is not a matter of doubt. For instance, leprosy was very frequent in the thirteenth century, when there were 2000 leprosy houses in France and 19,000 in Europe. At present this disease is localized in a few regions. In France sporadic cases are met with around Marseilles and Nice.

On the other hand, some diseases have made their appearance at a certain epoch, and do not seem to be destined to disappear in the near future. For example, the eruptive fevers were imparted in the sixth century. Although smallpox existed in China a thousand years before Christ, its occurrence in Europe was not mentioned until the year 570 A.D. by Marius, bishop of Avenches (Switzerland), and in 580 A.D. by Gregory of Tours. Measles, which dates from the same epoch, seems to have definitely settled among us. Scarlet fever was mentioned by Ingrassias in the sixteenth century. Finally, sudor anglicus appeared in England for the first time in the fifteenth century and ceased in 1551. The symptoms of the first epidemics, however, were very different from those presented by modern epidemics, the history of which begins in the eighteenth century (*suette picarde*, 1718–23). Therefore, some authorities, such as Hecker and Littré, have denied the identity of the two epidemics.

Passing to modern times, we find cerebrospinal meningitis, which did not appear until the nineteenth century. In 1831 cholera made its first appearance in Europe, and the following year it entered France. Since that epoch it has returned several times, always preserving the same clinical characters, but tending more and more to acclimate itself to our countries and to become localized in small endemic foci.

The symptomatology of infectious diseases has not remained invariable. The history of influenza reveals that the malady was formerly observed in the form of catarrhs and pulmonary localizations. At present it occurs also with nervous symptoms which, in some

cases, are the predominant or only manifestations, and may persist for months after apparent recovery. Similar remarks are applicable to pneumonia. This infection no longer presents the former frank, plain character. Its resolution is far more tedious, and several weeks after defervescence stethoscopic signs may be found which embarrass the physician and lead him to doubt the nature of the process.

The causes of all these changes are mostly unknown. A few conditions, however, have been determined.

At all times it has been noted that fatal epidemics were preceded by cosmic perturbations, great variations in pressure and temperature, earthquakes, and volcanic eruptions. At the present time we are unable to conceive the mode of action of these cosmic agencies.

We are a little better acquainted with the influence of social conditions. Infectious diseases change in frequency and form parallel to variations in the progress of civilization. During the warlike periods of humanity infections reigned as a result of traumatism, overwork, and crowding. During the periods of naval conquests we transported beyond the seas the maladies of our continent and imported various exotic infections.

Modern civilization has arrested the course of epidemics, and the advances of therapeutics have diminished their mortality. Vaccinations tend to abolish certain diseases, notably variola.

Some infections, however, persist with obstinate tenacity. Tuberculosis seems to be on the increase.

Although hygiene has diminished the frequency of infections, it has been less effective as regards intoxications. The latter become more and more numerous. Alcoholism tends to favor certain infections and to modify clinical types. The advances of civilization as a cause of growing excitation of the nervous system favor the development of cerebral manifestations, thus modifying clinical types. The pathology of the nineteenth century differs from that of preceding ages and will differ from that of the future. Infections are subject to the general laws of evolution, and, while we are unable to comprehend all the conditions which contribute to modify the clinical characters of diseases, we at least understand that they cannot remain immutable.

CHAPTER IV.

PATHOGENESIS OF INFECTIONS.

Rôle of Microbes in the Development of Infections. Importance of the Number. Variations of Virulence. Exaltation and Attenuation. Selective Harmfulness for Certain Organs or Tissues. Modes of Entrance of Microbes. Importance of the Mode of Entrance with Regard to Gravity and Symptoms of Infection. Modes of Action of Microbes. Discussion of Hypotheses. Rôle of Microbic Poisons. Study of Putrefaction Poisons and Gastrointestinal Poisons. Autointoxications of Gastrointestinal Origin. Toxins of Pathogenic Microbes. Local Action and General Manifestations Ascribable to These Toxins. Study of the Principal Toxins Produced by Pathogenic Microbes. The Poisons in the Infected Organism. Toxic Character of the Blood, Serum, and Urine. Urinary Toxins and Ptomains.

Role of Microbes in the Development of Infections; Role of Number. An infectious disease expresses the struggle engaged between an animal organism and a microbic agent. In order to understand the evolution of the disease we must study successively those modifications of the organism and of the microbe which favor or hinder the production of morbid phenomena.

Let us first consider the rôle of the microbe. It is now known that it is necessary to take into account both the quantity and the quality of pathogenic agents attacking the organism.

In the beginning of bacteriological studies, when an endeavor was made to differentiate infections from intoxications, it was thought that, contrary to what is true with regard to poisons, quantity was of no importance when the question was one of microbic virus. This was at the time when Davaine showed that one-millionth of a drop of blood derived from an animal infected with anthrax possesses sufficient virulence to cause death. The researches of Chauveau, W. Cheyne, and Bouchard have fully established the importance of quantity. Thus the guinea-pig, of all animals the most susceptible to tuberculosis, does not contract the infection unless eight hundred and twenty bacilli are introduced beneath its skin. With pus cocci far greater numbers are requisite.

Operating with proteus vulgaris, Watson Cheyne discovered that 6,000,000 of microbes injected beneath the skin do not produce any lesion; 8,000,000 cause the formation of an abscess; 56,000,000 give

rise to a phlegmon to which the animal succumbs within five or six weeks; 225,000,000 must be injected in order to cause death within twenty-four or thirty hours. Experimenting with staphylococcus upon rabbits, he found that 250,000,000 microbes are required to produce an abscess and to cause death, one milliard (1,000,000,000).

We have obtained quite similar results by inoculating into guinea-pigs cultures of staphylococcus aureus obtained from a phlegmon consecutive to erysipelas. An injection of 0.2 c.cm. produced a circumscribed abscess; 0.6 c.cm. caused edema, followed by a patch of sphacelus; with exfoliation of the slough the connective tissue and subjacent muscles were found to be necrotic. Finally, with 1 c.cm. an enormous invading edema was obtained which ended fatally in four or five days.

These facts are interesting because they show that inoculation of the same microbic cultures into the same region in animals of the same species gives rise to manifestations which vary in gravity and nature according to the dosage. The experimenter is thus able to produce, at will, abscess, gangrene, or fatal edema.

In all these experiments the microbes were injected beneath the skin. By varying the mode of introduction, different results are obtained. To produce suppuration with *staphylococcus aureus* it was necessary in the researches of Herman to inject 4 c.cm. to 5 c.cm. of the culture into the peritoneal cavity, 0.75 c.cm. to 1 c.cm. beneath the skin, 0.25 c.cm. into the pleural cavity or arachnoid space, 0.5 c.cm. into the veins, and 0.0001 c.cm. into the anterior chamber of the eye. The anterior chamber of the eye, therefore, is the most poorly protected part of the organism. The same is also demonstrated by the study of symptomatic anthrax. This virus, which is inoffensive to rabbits when injected hypodermically, causes speedy death when introduced into the anterior chamber of the eye.

Variations in the Virulence of Microbes. A fact of prime importance dominates the history of all infections, viz., the virulence of microbes is not fixed and unchangeable. It is modified by a vast number of circumstances of which several have been clearly determined.

As exaltation may be considered an adaptation to new biological conditions, it is conceivable that a microbe can be habituated to the living medium and develop more and more easily therein. Inoculations in series offer the best means of increasing pathogenic potency. On the other hand, cultivation in inert media is the surest method for diminishing pathogenic potency, and the more the culture medium

differs from the organic medium the more speedily is the virus attenuated. This weakening is more rapidly effected in mineral solutions than in bouillon, and more readily in bouillon than in blood serum or in defibrinated blood.

It is to be noted that a microbe exalted for one animal species is not necessarily so for others. We have studied a specimen of anthrax which, after successive passages through rabbits, had become, contrary to the rule, far more virulent for this animal than for the guinea-pig. In this connection we may cite the experiments of Pasteur, showing that the virus of hydrophobia is attenuated when inoculated into monkeys, as is evident from the increase in the period of incubation.

These results are not merely of theoretical interest. They explain certain facts which, at first, may seem incomprehensible.

In fact, under the habitual conditions of life, we see that viruses, by passage through the organisms of different animals, undergo such modifications as to puzzle the observer as to their origin. Thus, it is now demonstrated that tuberculosis is produced in all animals by a single bacillary species. The microbes have suffered changes, however, according as they have invaded mammalia or birds, thus constituting two varieties which have appeared to some observers as two different species. The bacillus exalted for birds is attenuated for mammalia, and *vice versa*.

The knowledge of these facts shows that inoculation into animals does not always yield results responding to the previsions of clinical observation. We cannot establish a diagnosis for man upon experimental results. Virulence being a contingent property, depending rather upon the invaded organism, it is conceivable that it should differ with each being under consideration.

Selective Injuriousness of Pathogenic Agents. Some of the pathogenic agents manifest an affinity for a certain organ or tissue in which they settle, and manifest no tendency to invade other parts. They are even incapable, at times, of emigrating from the organic territory to which they are habituated. Thus the microbe of mumps fixes itself in certain glands; the cholera vibrio multiplies exclusively in the intestine; the agent of hydrophobia invades the nervous system. Some specific bacteria, however, are apt to colonize more or less everywhere. Such, for instance, are the bacillus of glanders, the tubercle bacillus, and the agent of syphilis.

On the other hand, the non-specific bacteria are all capable of

developing in the most dissimilar parts of the organism. There is no tissue or an organ which cannot be invaded by the staphylococcus, streptococcus, pneumococcus, or colon bacillus.

Even these common agents, however, are in some degree capable of education, and acquire a special aptitude to live in a certain tissue. They become used to the biological conditions of that part of the organism, and no longer manifest any inclination to invade others. This fact was illustrated in a case of acute ascending paralysis which the author studied with Dr. Josué.[1] The manifestations were due to a pneumococcus which, when inoculated into animals, produced spinal symptoms. This microbe, then, behaved as if it had acquired a sort of selective harmfulness for the nervous tissues by virtue of its first passage through the spinal cord of our patient.

Our idea was taken up and developed by Drs. Bezancon and Labbé,[2] who collected a certain number of facts showing that microbes obtained from an organic lesion when introduced into animals localize themselves in that part which was attacked in the human subject. Thus, Dreschfeld produced endocarditis in rabbits which were inoculated with a streptococcus derived from an infectious endocarditis.

These facts prove that microbes may acquire the habit of colonizing in a certain organ or tissue in preference to others. It may now be asked why a microbe, for the first time, localizes itself at a certain point of the economy. Several conditions may intervene. One of these is the mode of entrance of the pathogenic agent.

Modes of Entrance of Infectious Agents. Certain microbes possess such a high degree of virulence that their introduction into the organism is invariably followed by the development of a fatal disease. No matter what the mode of introduction may be, the result is the same. Such, for instance, is the case observed when chicken cholera is inoculated into the rabbit. This fact, however, is exceptional. In most cases infection is modified according to the channel by which the virus enters.

The usual modes of entrance of morbific germs are four: the skin and the subcutaneous cellular tissue, the respiratory passages, the alimentary canal, and the genito-urinary apparatus.

[1] Roger et Josué. Un cas de paralysie ascendante aiguë. Presse médicale, July 27, 1898.

[2] Bezancon and Labbé. Role de l'accutumance dans la determination des localisations microbiennes. Presse médicale, March 7, 1900.

Infections of Cutaneous Origin. In this connection, the first question to be asked is whether pathogenic agents are capable of invading the organism through the unbroken skin. As a rule, they are not. The rule is not, however, without exceptions, especially as regards the mucous membranes. Let us first see what occurs with the skin.

Ancient observers admitted that viruses could penetrate through the intact epidermis. The fact seems to be real with regard to certain pus cocci, as is demonstrated by the frequency of small pustules upon the back of the hands of anatomists. The microbes are undoubtedly introduced through the sebaceous glands. Roth, by rubbing the skin of guinea-pigs with a mixture of fat and a bacteria culture, was able to produce abscesses. When experimenting with anthrax he witnessed the production of a local edema which in some cases proved fatal. No result, however, was seen when the culture was simply deposited upon the skin without any friction. By similar procedures, Babes succeeded in inoculating glanders into guinea-pigs through the healthy skin.

When infection occurs in the skin the lesion often remains limited to the spot. This is what happened in Roth's experiments with the anthrax bacillus. The same is demonstrated by clinical observation. Lupus and anatomical tubercles manifest hardly any tendency to generalization. The fact may be due to the special structure of the skin. It may also be explained by the temperature of the skin, which is too low to favor active vegetation of the microbic agent.

Subcutaneous Inoculations. In most cases the virus is deposited beneath the skin, either in the cellular tissue, or even more deeply in the muscles and nerves.

With the same virus the results may differ according to the point of subcutaneous inoculation. Thus the regions where the connective tissue is dense are not very favorable for the propagation of microbes. If a very energetic virus, such as that of symptomatic anthrax or of gaseous gangrene, is inoculated into the tip of the tail or the ear, only a local lesion capable of causing the loss of a part of the organ results, but ending in recovery. The density of the cellular tissue and the low temperature of the region hinder the vegetation of the microbes and insure survival of the animal, which would certainly perish if the inoculation were practised at some other point.

The results of inoculation also vary according to the depth of the wound. In this respect nothing is more interesting than the study

of hydrophobia. Helman discovered that the adipose tissue offers an unfavorable channel of absorption for the hydrophobic virus. Fat dogs, therefore, resist hypodermic inoculation, while the young and thin ones mostly perish. When the virus is introduced into the subcutaneous cellular tissue of rabbits, 75 per cent. of the inoculated animals die. If the injection is made into a muscle, the mortality rises to 85 per cent. If sectioned muscles are operated upon, and the virus is introduced between the muscular fibres, all the animals succumb.

The deductions which may be drawn from these experiments are self-evident. The great danger attending deep wounds is in part due to the introduction of the virus into the subcutaneous muscles and nerve fibres. Numerous experiments have shown that the hydrophobia virus follows the nerve fibres in order to reach the nerve centres, where its localization gives rise to clinical manifestations of the most fearful character. Hence the more richly the wounded part is supplied with nerves the more certain is contamination and the shorter the period of incubation.

Infections through the Mucous Membranes. The mucous membranes are more easily penetrated by microbes than the skin. The pathogenic agents often leave no trace of their passage or, after giving rise to some slight and curable lesion, invade the neighboring lymphatic ganglia. By depositing tuberculous sputum in the lower conjunctival cul-de-sac, without any traumatism of the mucous membrane, Cornet observed no more than a little redness at the point of inoculation. The cervical glands, however, became caseated, and microscopic examination revealed in them the presence of numerous tubercle bacilli. He operated upon the mucous membranes of the nose, gums, penis, and vagina with similar results.

Infection through the Respiratory Passages. The respiratory tract is believed to be a frequent channel of contamination. Many authors assert that the germs of eruptive fevers, especially those of measles and variola, are introduced by this route.

On the other hand, it has been remarked that while infection is grave when it occurs spontaneously, it is generally mild when it originates by subcutaneous inoculation. This is demonstrated by the practice of variolization.

In studying the respiratory mode of entrance, authors have chosen particularly the bacillus anthracis. Flugge and Wyssokowicz asserted that the bacillus could not pass through the intact lung. Such

conclusion can no longer be accepted in view of the researches of Buchner, Muskalbluth, and Enderlein. These authors made numerous experiments, consisting in the injection of the virus directly into the trachea, or in causing it to be breathed in the shape of dried powder. Most of the animals—rats and guinea-pigs—died.

Buchner produced a general infection, without any pulmonary alteration, by causing animals to inhale anthrax spores. By employing the bacilli themselves he often observed red hepatization and, in these cases, the animals survived. This result is explained by the fact that the adult microbes, which are comparatively weak, succumb and transude an irritating substance, while the spores give birth to vigorous bacilli of great resistance. The local lesion is, therefore, the result of the organic resistance, though this is not always sufficient to prevent infection. This is further illustrated by the study of the pneumococcus. If this microbe is introduced into the trachea of an animal very sensitive to its action, such as the rat or the rabbit, no pulmonary lesion is obtained, but death supervenes as the result of a general infection—that is, a veritable septicemia. If a more resistant animal is experimented upon, the dog, for instance, the result is a fibrinous pneumonia. The same is true with regard to man. The pneumococcus is present in the oral cavity of many healthy persons. When a disturbing influence diminishes the organic resistance a pneumonia is produced expressing the reaction of the individual against the pathogenic agent. The same remark is also applicable to diphtheria.

In the majority of cases the bacilli of tuberculosis invade the organism through the respiratory organs. The experiments of Tappeiner demonstrate that dogs, which are quite resistant to tuberculosis, easily contract this malady when they inhale dried and pulverized sputa. The local lesion, however, may be lacking or promptly repaired. The bacilli pass through the lung without leaving any lasting trace of their passage, and take up their abode in other parts of the organism. They may cause a general infection or be arrested in the mediastinal ganglia. The latter event is frequently observed in children who are so often victims of seemingly primary tracheobronchial adenopathies.

It is not to be assumed, however, that the respiratory passages represent a door open to all infections. The bacilli of symptomatic anthrax and of gaseous gangrene may be introduced into the trachea with impunity. They give rise to no disturbance, for the reason,

perhaps, that these agents are anaërobic. It must further be remembered that in this organ, as in the rest of the economy, important means of defense, including phagocytosis, exist.

Infection by the Alimentary Canal. Under normal conditions the digestive tract contains a prodigious quantity of microbes, of which several are pathogenic. Owing, however, to the numerous modes of protection with which this canal is endowed, the presence of the microbes gives rise to no disturbance. Nevertheless, infection is possible, though here it is more difficult than through the respiratory passages. While the inhalation of the *bacillus anthracis* kills most of the animals—rats or guinea-pigs—its ingestion is, as a rule, well resisted.

The alimentary canal may be the starting point of a great number of infectious diseases. It will suffice to mention typhoid fever, dysentery, and cholera.

Tuberculous lesions are also frequently observed in the digestive canal and are generally secondary to deglutition of sputa. They may, however, be primary, as a result of ingestion of contaminated food and, particularly, milk drawn from cows affected with mammary tuberculosis.

Tuberculosis of intestinal origin may appear in two different forms: 1. The localizations are sometimes found in the canal and the mode of entrance is readily recognized. 2. At other times no intestinal lesion is discoverable, since the bacilli have passed onward to colonize in the mesenteric ganglia, peritoneum, or even the lungs.

Of all the microbes normally inhabiting the intestine the most interesting is undoubtedly the *bacillus coli communis*. The study of the diseases which it is capable of producing is the finest illustration of the surprising modifications undergone by a microbe. An innocent guest in most human subjects, under influences as yet vaguely recognized, it may acquire noxious properties and give rise to the most varied intestinal disturbances—simple diarrhea, dysenteriform diarrhea, or some form of cholera. It may even leave the intestine and produce either septicemias or bronchopneumonias; or, by ascending the biliary passages, induce a suppurating angiocholitis.

Migration may occur when there is some obstacle to the course of fecal matters. Artificial occlusion of the rectum suffices to cause bacteria to pass into the general circulation (Possner and Lewin). The same phenomenon is observed in the course of certain infections and intoxications. According to Chvostek and Egger, after a mala-

rial paroxysm and after the injection of tuberculin, various microbes can be found in the urine, particularly the colon bacillus, which probably comes from the intestine. The researches of Beco, Wurtz, and Hudelo demonstrate that poisoning by tartar emetic, cantharidin or alcohol likewise favors penetration of bacilli. Authors have thus been led to attribute to infection a rôle in the origin of alcoholic cirrhosis.

Infection by the Genito-urinary Organs. Under normal conditions microbes do not pass beyond the navicular fossa. They may often, however, invade the rest of the urethra after catheterization or after sexual intercourse. In the latter instance, several infections may be transmitted, from gonorrhea to tuberculosis. The infection may pass from the urethra into the bladder, but scarcely ever beyond that point. As has been established by Albarran and Halle, numerous microbes are very frequently found in the bladder. Only one, however, the bacillus coli, is capable of advancing to the renal pelvis and kidneys. It is interesting to note that this microbe manifests the same tendency to ascend to the liver along the excretory passages and contrary to the current of the bile. Angiocholitis and suppurative nephritis represent two perfectly analogous processes.

In women protection against microbes is quite efficacious. Even after parturition, infections of genital origin are difficult. Experiments have shown that the uterus of a puerperal woman possesses a special resistance. Certain microbes, however, notably the streptococcus, can invade it, producing one of the forms of puerperal fever.

Infection by the Organs of Sense, Serous Membranes, and the Nervous System. It has already been stated that the conjunctiva may serve as a channel of entrance, but the anterior chamber especially offers an important route of introduction, at least from an experimental standpoint. Thus, for instance, hydrophobia as surely develops when the virus is deposited at this point as when it is introduced into the nervous system. Cohnheim and Baumgarten have discovered that this is a very certain channel for the introduction of tuberculosis.

The serous membranes are not a route habitually open to infections, except in cases of traumatism. Experimenters frequently employ it for the introduction of microbes. At all events, the results are similar to those obtained with inoculations into the mucous membranes. In some instances the animal resists; in others a gen-

eral infection is produced without any lesion at the point of injection. At other times a local lesion is caused which may or may not be followed by general infection.

Lastly, another channel for contamination is the nervous system. The agent of hydrophobia propagates through the nerves, as both clinical observation and experimental researches have demonstrated. In this way the virus reaches the nerve centres. It is conceivable, therefore, that the nearer the affected nerve is to the spinal bulb the shorter the period of incubation, and, furthermore, the first manifestations will vary with the region primarily contaminated.

Infection by the Vascular System. Whatever the route by which microbes are introduced into the organism, they either remain at the point where they are primarily deposited or invade the organism. In the former case they may be speedily destroyed or give rise to the formation of a local lesion, which often represents a means of defense opposed by the organism. However, the microbes multiplying at the point of the lesion at times secrete extremely active toxic substances, and in this manner give rise, not to an infection, but to a more or less serious intoxication which is at times fatal. This is what occurs in gaseous gangrene, diphtheria, and cholera. These maladies should, therefore, be considered as bacteriotoxemias.

When infection is generalized, whether a local lesion is present or not, the microbes penetrate by the bloodvessels or the lymphatic channels. In the latter case they are first arrested by the glands, the hypertrophy of which testifies sufficiently as to their increased activity. The process may stop here or may pass beyond the barrier opposed by the glands and spread in the blood.

Under natural conditions the blood is almost always secondarily invaded. Direct introduction into the circulation occurs only in the fetus, since the pathogenic agents cannot reach it otherwise than by the sole point of contact which it has with the external world —that is, the umbilical vessels. Infection then assumes a special aspect imposed by its localizations. It is thus conceivable that the liver should be profoundly altered in inherited syphilis and that the various stages should not be separated, as in the adult. There is generalization from the first; hence, the absence of primary lesions and confusion of secondary and tertiary stages.

Whether directly introduced into the veins or secondarily invading the circulatory system, microbes do not remain in the blood. They rapidly leave this unfavorable medium and take refuge in the tissues

and organs. They do not, however, distribute themselves equally in all the tissues, nor do they affect all the organs in the same manner. The results vary according to the species or variety under observation. If a tissue is already altered, whether by traumatism or previous disease, the microbes will preferably settle in those parts of lessened resistance. It is, therefore, possible, in experimental researches, to cause a pathogenic agent to colonize at this or that point of the organism, and thus create, at will, nephrites, endocardites, osteomyelites, and infectious arthrites.

Mode of Action of Pathogenic Microbes. The causes favorable to infection having been described, it remains to study in what manner microbic development is followed by morbid disturbances.

Several theories have been advanced. In the first, a mechanical theory, it is assumed that the microbes act simply like foreign bodies; by obstructing the capillaries they hinder the functions of the organs. This conception is hardly deserving of discussion, especially in view of the fact that the microbes often remain localized in some organ or tissue, or at some point of very limited extent, as in the case of diphtheria, tetanus, and symptomatic anthrax.

In the second theory it is assumed that there is a struggle for life. It is supposed that the microbes and the cells of the organism vie with each other for the possession of the alimentary materials and oxygen carried by the blood. When the question is one of a microbe like the diphtheria bacillus, which lives upon the surface of a mucous membrane, or of an anaërobic agent, such as the bacillus of tetanus, the oxygen of the blood is not needed for the development of the pathogenic agent. As to the use of nutritive materials, how much of them can the microbes consume? We have no information concerning this point. However, notwithstanding their active multiplication, microbes weigh too little to give strength to the opinion that their development starves the economy. The problem is more complex. In order to nourish itself, every being is forced to secrete ferments which transform or modify the alimentary substances. Microbes are subject to this law and produce amylolytic, inversive, and proteolytic ferments. These ferments give rise to substances which may serve their nutrition, but may prove harmful to the invaded organism. As in every living cell a double process—assimilation and *disassimilation*—goes on in the interior of microbes. The products of bacterial *disassimilation*, useless to the microbes, are

rejected into the interstitial plasma and into the blood, and represent other noxious substances.

Moreover, the substances of which the microbic protoplasm is composed are not harmless. This also is the application of a general law. The extracts of all tissues give rise to morbid phenomena when injected into animals. These manifestations, which occur even when animals of the same species are operated upon, are much more marked when different species are employed. This is equally true with regard to bacteria. Their protoplasm contains toxic substances which may readily diffuse after their death, or perhaps even during life.

We conclude, therefore, that infectious agents exert only a mechanical influence of secondary importance. They give rise to nervous reactions, not by crowding the tissues, but through the agency of noxious substances which they produce and pass into the blood. As already stated, infection is a chapter of the history of intoxications.

Microbic Poisons.

Putrid Poisons. Before the discovery of pathogenic microbes, at an epoch when the nature of putrefactive agents was not even suspected, interesting results had already been obtained in the study of poisons produced by fermentations.

At the end of the eighteenth century Seybert[1] demonstrated that the putrefaction of pus, serum, and infusions of meat developed in these fluids a high degree of pathogenic power. He pointed out, for instance, that the intravenous injection of 20 c.cm. of putrefied serum into a dog produced vomiting and convulsions, ending in death within a few hours.

The question was taken up by Gaspard,[2] physician at St. Etienne, who pursued a series of very remarkable researches, the results of which were confirmed and completed by Magendie, Virchow, Stich, and, above all, by Panum, who, in 1856, isolated a poison the effects of which were comparable to those of the toxic substances above mentioned.

It is not sufficient, however, to point out the toxicity of putrid substances. The very element upon which their noxious action

[1] Seybert. Ueber die Faulniss in Blute an lebenden thierischen Körper. Berlin, 1758.

[2] Gaspard. Mémoire physiologique sur les maladies purulentes et putrides. Journal de la phys., 1822, 1824.

depends must be discovered. The bodies originated during the process of putrefaction are excessively numerous and, moreover, vary according as the substances are exposed to the open air or kept in closed vessels; according to the time putrefaction has lasted; according to the nature of the materials undergoing the process, etc. The following table, nevertheless, presents the principal substances:

- Gas
  - hydrogen, sulphuretted hydrogen, phosphorated hydrogen, protocarbonated hydrogen, ammonia, sulphohydrate of ammonia.
  - carbonic acid.
  - phosphorated gas, vaguely known (phosphins).
- Acids
  - volatile gases
    - formic (traces).
    - acetic.
    - butyric (very abundant).
    - valeric.
  - of the oleic series
    - acrylic.
    - crotonic.
    - palmitic.
    - oleic.
  - polyatomic
    - glycolic.
    - lactic.
    - oxalic.
    - succinic.
- Aromatic substances
  - indol.
  - phenol.
  - skatol.
  - paracresol, orthocresol.
  - acids
    - phenylacetic, pyroxylphenylacetic.
    - phenylpropionic, paroxylphenylpropionic.
- Albuminoid substances
  - albuminates.
  - peptones.
- Amidate bodies
  - leucin, leucein.
  - tyrosin.
  - xanthin, hypoxanthin.
- Organic bases
  - complex amido bodies.
  - methylamin, trimethylamin, etc.
  - ethylendiamin, amylamin, etc.
  - alkaloids or ptomains.

Finally, the residues of putrefaction are rich in earthy and ammoniacal salts, in fats, and often in nitrates.

So far as the gases are concerned, it is now known that they are not responsible for the toxicity of putrid matters. The same is true of fatty acids, aromatic substances, and amido bodies. There remain the albuminoids and the bases. According to Panum, toxicity must be attributed to the former group. Later came a series of very notable contributions, due to Nencki, Maas, and, above all, Brieger, who thoroughly studied the bases of putrefaction. Selmi[1] called them ptomains in order to indicate their cadaveric origin. He recognized that these ptomains are very numerous; that some are inoffensive and others toxic; that they resemble vegetable alkaloids;

[1] Selmi. Ptomain ad alcaloide cadaverici. Bologna, 1881.

that they cause pupillary disturbances, cardiac irregularities, narcosis or convulsions, and produce death by arrest of the heart in systole.

We cannot sum up all the works published on this interesting subject. Prof. Gautier, who was first to point out the existence of animal alkaioids, has several times returned to their study. Brieger[1] took up the complete study and reported a number of very remarkable facts. He assumes that at the beginning of all putrefaction, lecithin ($C_{44}H_{20}NPO_9$) is broken up into its components, and the oxyethylic base, cholin ($C_5H_{15}NO_2$), a substance of little toxicity, gives rise to a vinylic base, nervin ($C_5H_{13}NO$), a highly toxic body which is produced simply by subtraction of one molecule of water. The transformation of lecithin is readily accounted for by the great fragility of its highly complex molecule. It is, however, difficult to say whether the transformation of cholin is due to the reducing properties of the tissues which acquire so great an energy immediately after death, or whether it is already the work of microorganisms.

However that may be, here is a highly toxic base originated at the beginning of putrefaction. Brieger's researches have established that nervin is particularly active for the cat, which is killed by a few milligrams of it, while as much as four centigrams are required to kill a rabbit. Aside from nervin, there are two other bases: neuridin ($C_5H_{14}N_2$), which is not toxic, and methylguanidin (Brieger), which is tetanizing. There is also parvolin ($C_9H_{13}N$), found by Gautier and Etard in the putrid flesh of the horse; collidin, hydrocollidin, and two other bases isolated by Dr. Pouchet and having the formulæ: one, $C_7H_{18}N_2O_6$; the other, $C_5H_{12}N_2O_4$. These bodies are very toxic. Harmless bases, such as corindin ($C_{10}H_{15}N$), are also encountered. On the whole, the convulsifying alkaloids are dominant.

Brieger has established that the alkaloids produced in the human cadaver vary with the time elapsed since the moment of death. The first one is cholin, which appears as early as the first or second day and disappears toward the seventh day. On the third day neuridin is produced, which disappears toward the end of the second week. At the same time cadaverin may be isolated, which increases with the progress of putrefaction; then, toward the fourth day, appear

[1] Brieger. Untersuchungen über Ptomaine (3 pamphlets). Berlin, 1885–86.

putrescin, which is very abundant toward the fifteenth day, and saprin. These bases are not all toxic: cholin alone, when injected in high doses, produces a few symptoms resembling those provoked by muscarin.

The truly toxic substances appear toward the seventh day. At this stage, aside from trimethylamin, which is of little toxicity, two venomous bases are produced, of which considerable quantities may be collected toward the fifteenth day. One, the less active, causes only alvine evacuations; the other, mydalein, the chemical formula of which has not yet been determined, is extremely powerful.

When injected into guinea-pigs and rabbits, mydalein causes salivation and lacrymation. The pupils dilate, the ears are congested, and the rectal temperature is raised 1.8° to 3.6° F. (1° to 2° C.). If the dose reaches five milligrams in the guinea-pig, profuse diarrhea, exophthalmos, and then paralysis are observed; respiration becomes difficult, the temperature falls, and death supervenes, the heart being arrested in diastole.

Ehrenberg has discovered several bases in decayed fish, notably cholin, neuridin, methylamin, and dimethylamin. The most important body, however, is ptomatropin of v. Aurep, of which two milligrams cause, in a rabbit, mydriasis, convulsions, and death by arrest of the heart.

Neuridin and trimethylamin are likewise encountered in putrid milk and cheese; also a base discovered by Vaughan and designated tyrotoxin.

As has already been stated, ptomains differ notably according to the time at which the products of putrefaction are studied. Some appear and later disappear, to be succeeded by others. The chemical researches which have revealed these facts, however interesting they may be, ought to have been completed by bacteriological studies. It is, in fact, a question whether these diverse ptomains are produced during the various phases of the life of the same microbes, or whether their successive appearance and disappearance depend upon different microbes which destroy or transform the substances already produced by their predecessors.

Although we do not know exactly the rôle of ferments in the genesis of ptomains, we are better acquainted with the influence exerted by the media. It is known that certain bases are encountered in all putrefactions, for instance, neuridin, while neurin is found only in the putrefying flesh of mammalia and muscarin in that of

decayed fish. Likewise, gadinin, ethylenediamin, and trimethylamin are formed at the expense of the flesh of fish. Finally, dimethylamin has thus far been encountered only in the putrefaction of gelatin or of yeast.

Kostiurine and Krainsky very justly remark that the toxicity of the products of putrefaction is in direct ratio to the chemical complexity of the substances undergoing putrefaction. More poison is yielded by meat than by bouillon, and more by bouillon than by saline solutions. Toxins are most abundant from the fifth to the thirtieth day. Furthermore, toxins insoluble in alcohol are more active than those soluble in this fluid. This last fact clearly shows the importance of non-alkaloidal poisons.

There is no doubt that whatever cause hinders or favors the development of microbes also hinders or favors the development of putrid poisons. It will suffice, in this respect, to recall the influence of heat and electricity. As to the rôle played by oxygen, opinion is divided. An important fact established by Kijanisin has not, perhaps, been sufficiently considered. According to this author, a greater amount of ptomains are produced in contact with air than when the process of putrefaction takes place without air. But the ptomains are then less toxic and less stable; they, therefore, rapidly disappear.

All the principal ptomains actually known are presented in the table below, following Prof. Gautier's classification:

Methylamin, CH_5N,	Bocklisch,	Decayed fish,	Non-toxic.
	Wurtz,	Normal blood,	"
Dimethylamin, C_2H_7N,	Brieger,	Putrid yeast,	"
Trimethylamin, C_3H_9,	Ibid.	Decayed fish,	Convulsions.
Triethylamin, $C_6H_{15}N$,	Ibid.	Ibid.	"
Propylamin, C_3H_9N,	Ibid.	Putrid gelatin,	"
Butylamin, $C_4H_{11}N$,	Gautier and Mourgues,	Cod-liver oil,	Stupefying and convulsifying poison.
Isoamylamin, $C_5A_{13}N$,	Müller and Hesse,	Putrid yeast,	Stupefying and convulsifying poison.
Amylamin, $C_5H_{13}N$,	Gautier and Mourgues,	Cod-liver oil,	Polyuria; convulsions.
Hexylamin, $C_6H_{15}N$,	Ibid.	Ibid.	" "
	Hesse,	Putrid yeast,	" "
Neuridin, $C_5H_{14}N_2$,	Brieger,	Fresh brain;	Non-toxic.
		all putrefactions,	Ibid.
Saprin, $C_5H_{14}N_2$,	Ibid.	Cadavers,	Ibid.
Cadaverin, $C_5H_{14}N_2$,	Brieger,	Cadavers,	Ibid.
	Bocklisch,	Decayed fish,	Ibid.
	Brieger,	Cadavers,	Local action, inflammation necrosis.
Putrescin, $C_4H_{12}N_2$,	Bocklisch,	Herring,	Local action, inflammation necrosis.
Ethylenediamin, $C_2H_8N_2$,	Brieger,	Putrid codfish,	Nasal flux and mydriasis; dyspnea and death.
Methylguanidin, $C_2H_7N_3$,	Ibid.	Decayed fish,	Excitation, then paralysis of the nervous system.

Nevrin, $C_5H_{13}NO$,	Ibid.	Tainted meat,	Myosis; salivation; paralysis; death. Atrophy (Carvello).
Cholin, $C_5H_{15}NO_2$,	Ibid.	Ibid.	Like muscarin, but action slight.
Muscarin, $C_5H_{15}NO_3$,	Ibid.	Putrid codfish,	Lacrymation, salivation, convulsions.
Mydotoxin, $C_6H_{13}NO_2$,	Ibid.	Cadavers,	Lacrymation, salivation convulsions.
Mydin, $C_8H_{11}NO_2$,	Ibid.	Ibid.	Non-toxic.
Gadinin, $C_7H_{16}NO_2$,	Ibid.	Decayed fish,	"
Methylgadinin, $C_8H_{18}NO_2$,	Brieger,	Tainted meat,	Tetanizing poison.
Collidin, $C_8H_{11}N$,	Nencki,	Pancreatic digestion,	" "
	Œ.de Coninck	Putrid pulp,	" "
Hydrocollidin, $C_8H_{13}N$,	Gautier and Etard,	Decayed fish,	Trembling, convulsions, arrest of heart in diastole.
Parvolin, $C_9H_{13}N$,	Ibid.	Ibid.	Very toxic.
Coridin, $C_{10}H_{15}N$,	Guareschi and Mosso,	Putrid fibrin,	" "
	Œ. de Coninck	Putrid pulp,	" "
Hydrolutidin, $C_7H_{11}N$,	Gautier and Mourgues	Cod-liver oil,	Trembling paralysis.
Scombrin, $C_{17}H_{38}N_4$,	Gautier and Etard,	Decayed fish,	Trembling paralysis.
Morrhuin, $C_{19}H_{27}N_3$,	Gautier and Mourgues	Cod-liver oil,	Diuretic.
Asellin, $C_{25}H_{32}N_4$,	Ibid.	Ibid.	Convulsions; death.
Morrhuic acid, $C_9H_{13}NO_3$,	Ibid.	Ibid.	Convulsions; death.
" " $C_7H_{18}NO_2O_6$,	Pouchet,	Putrid meat,	Convulsions; death.
" " $C_5H_{12}N_2O_4$,	Ibid.	Ibid.	Convulsions; death.
" " $C_{14}H_{20}N_2O_4$,	Guareschi	Ibid.	Non-toxic.
" " $C_5H_{11}NO_2$,	Salkowski,	Ibid.	Ibid.
Mydalein, $C_5H_{11}NO_2$,	Brieger,	Human cadavers,	Fever; glandular hypersecretions.
Ptomatropin, $C_5H_{11}NO_2$,	Aurep,	Fish and meat poisons,	Action analogous to that of atropin.
Ptomatocurarin, $C_5H_{11}NO_2$,	Harkawy,	Putrid yeast,	Like curare.
Ptomatoconicin, $C_5H_{11}NO_2$,	Otto,	Cadavers,	Like conicin.
Ptomatoveratrin, $C_5H_{11}NO_2$,	Brouardel and Boutmy,	Ibid.	Like veratrin.
Tyrotoxin, $C_5H_{11}NO_2$,	Vaughan,	Spoiled milk and cheese,	" "

Gastrointestinal Putrefactions. The foregoing study of putrid poisons and the facts concerning their production outside the organism find numerous applications in the history of gastrointestinal putrefactions.

The microbes of the alimentary canal, having entered with beverages and aliments, must evidently be the same as those which are encountered in putrefactions in the free air. Although it is comparatively easy to determine the changes alimentary substances undergo outside of the organism through the agency of bacteria, the problem is far more delicate when the study of such phenomena occurring in the intestine is undertaken. Here substances rapidly disappear by absorption, and, on the other hand, it is difficult to decide which changes are due to digestive juices secreted by the organism and which alterations are dependent upon bacterial action. Peptones,

which are abundantly produced in both cases, may be mentioned as an example. It may, therefore, be erroneous to consider all microbic products harmful. Certain micro-organisms are possibly useful and must be considered as collaborators of the individual whom they inhabit. Dr. Duclos asks whether microbes do not accomplish a complementary digestion nearly as important as digestion properly so called. In fact, it is certain that several substances are not transformed without the intervention of microbes. Such is notably the case with cellulose. It can be seen, therefore, how complex this problem is and how interesting it would be to exactly determine the rôle, importance, and signification of microbic fermentations in the processes of digestion and nutrition.[1]

We shall, therefore, endeavor to give a résumé of our knowledge of this subject.

As far as the carbohydrates are concerned, transformation by the digestive juices consists in the production of dextrin and sugars (glucose, levulose, maltose). The microbes form analogous substances by saccharifying the starch or by interverting saccharose. Fermentation may, however, go further and give rise to ethylic alcohol. This fact is of great interest, since it perhaps accounts for the presence of alcohol in the liver and brain of animals which have never ingested this substance (J. Bechamp, Rajewski).

There is another series of bodies due to the action of figurate ferments, namely: lactic, acetic, butyric acids, etc. These acids are especially abundant in herbivora.

Microbes are able to break up neutral fats, but they act more particularly upon albuminoids. Along with peptones, attributed to the action of the pancreatic juice, there are amidate acids, leucin, tyrosin, hypoxanthin, aspartic acid, and cinnamic acid; bodies of the aromatic series, indol, phenol, skatol, and, finally, various gases, carbonic acid, hydrogen, sulphuretted hydrogen, and ammonia. We have already stated that all these bodies are likewise produced when albuminoid substances undergo putrefaction. It is important to determine what modifications are properly due to the pancreatic juice. The question has been studied by Kühne. By accomplishing artificial digestion in a medium containing 2 per 1000 of salicylic acid, he prevented the development of germs and observed the production of peptones and amidate acids, but he found no aromatic

[1] Roger. Art. Physiologie de l'intestin. Dict. encyclop. des sc. médicales, Paris, 1889, 4 série, t. xvi.

substances or gases. Other experimenters have obtained the same results. It may, therefore, be stated that the intestinal gases and aromatic substances depend upon the life of the microbes. This fact explains the absence of these substances in the intestine of the fetus and the newborn.

Toxicity of Fecal Matters. Prof. Bouchard was the first to show, in 1882, that fecal matters contained alkaloids, some of which are soluble in chloroform and others in ether. Fecal matter, studied without separation of soluble substances, is highly toxic. According to Prof. Bouchard, the extract of seventeen grams is sufficient to kill a rabbit of one kilogram with diarrhea and convulsions. The poisons are evidently manifold. A great part of the noxious effect is due to potassium salts and ammonia. In fact, if these salts are eliminated, the extract of 298 grams of feces is required to kill the animal. It is certain that these figures have no absolute value and that the toxicity of the matters is not constantly the same.

From a toxicological standpoint it may be stated that alcoholic extracts are generally less active than aqueous. As to the toxicity of diarrheal feces, those obtained during the stationary period are the most noxious. The feces of a patient already convalescent have been found less toxic than normal fecal matters.

Variations of Gastrointestinal Putrefactions. The intensity of gastrointestinal putrefaction varies considerably with the diet. Veal, particularly that of very young calves, forms in the intestine a sort of jelly which is difficult of absorption and offers a favorable pabulum for microbes. On the other hand, milk diet checks putrefaction (Biernachi) by reducing the number of bacteria (Gilbert and Dominici). Even outside the organism this fact has been observed. If milk is added to a mixture of muscles and pancreas, at the end of four days neither indol, skatol, leucin, nor tyrosin is found (Winternitz).

Among the disturbances arising from autointoxications of intestinal origin the most serious are those following ingestion of putrefied meat, often characterized by grave and at times fatal symptoms. The best known type of these disturbances is botulism or allantiasis. It has been well studied in Germany where alimentary intoxications are frequent from the use of imperfectly cooked sausage, which not infrequently contains a great amount of ptomains and microbes.[1]

[1] For the study of alimentary intoxications, consult: Netter, Des poisons chimiques qui apparaissent dans les matières organiques en décomposition, et des maladies qu'ils

Alimentary poisoning does not, however, always assume the grave appearance observed in typical cases of botulism. Simple gastro-intestinal disturbances often follow the ingestion of slightly altered meat or other tainted food. There is vomiting, though not in every case, and especially diarrhea, which is profuse and extremely fetid. In these instances the process is one of intoxication, the elements of which originate in the intestine under the influence of microbes contained in the food.

Dr. Cassedebat[1] found in preserves numerous toxic alkaloids, several of which resisted boiling. Under the influence of alkaline bicarbonates, some of them produced a penetrating and persistent odor which is also found in the air exhaled by animals which have ingested these toxic bases.

Tainted fish and preserved fish represent another source of danger. Brieger, Gautier, and others have discovered numerous ptomains engendered in putrefied fish. Disturbances are frequent as a result of the ingestion of sardines, salmon, and particularly codfish. The process is the same as in the case of meat. We must take into account both the microbes and the ptomains which are secreted by them, as was demonstrated by Duvillier.

Crustaceans and mollusks decompose more easily than fish. The disturbances produced by tainted prawn and crabs have long been described. One of the most remarkable observations is that reported by Dr. Rapin (of Lausanne) in 1877. Crabs were consumed one day without inconvenience; the following day nine persons ate some. After a period of incubation of sixteen to fifty-five hours, those who had eaten began to vomit, had sanguinolent diarrhea, and presented a scarlatinoid eruption. One of the victims died on the twenty-third day with typhoid-like symptoms. A dog which ingested some of the crabs manifested no disturbance.

Such accidents are most often due to preserved lobster, which, while always unhealthful, is particularly dangerous when the container has been open for a day or two.

A ptomain, tyrotoxin, as already stated, is found in tainted milk. The same is encountered also in spoiled cheese, ice-cream, ices, and

peuvent provoquer. Arch. gén. de médecine, 1884; Roger, Fermentations et putréfactions intestinales. Gaz. des hôpitaux, March 31, 1888. Polin et Labit, Etude sur les empoisonnements alimentaires. Paris, 1890. (This is a very complete and highly interesting monograph.)

[1] Cassedebat. Bactéries et ptomaïnes des viandes de conserves. Revue d'hygiène, 1890, p. 659.

certain cakes. Altered milk causes disturbances, especially in children, and at times even infantile cholera.

Condensed milk quite often becomes altered and liberates gases which force off the cover of the can. Dr. Cassedebat, who has made a study of preserved milks, discovered no microbes in them, but only aspergillus and a few mucedinea. Although harmless, the preparation is not then fit for consumption.

Autointoxications of Gastrointestinal Origin. No matter how produced, a diarrhea is attended by intense intestinal putrefaction, as we have already reported. Are the poisons thus formed absorbed? Stich believed they were not. At the present day, however, there can be no doubt that they are. The terrible offensiveness of the breath suffices to demonstrate this. In such cases Prof. Bouchard was able to discover considerable quantities of ptomains in the feces and urine. He found as much as 15 milligrams per 1000 grams of fecal matters, while the urine contained fifty times more than under normal conditions. In more serious instances of diarrhea, fermentation at times produces ammonia which may give rise to capillary thrombosis (fermentative thrombosis of Hlava), and, secondarily, to pseudomembranous enterites, with superficial necrosis of the mucous membrane.

While putrefaction is increased in cases of diarrhea, in cases of constipation, on the other hand, stagnation of the fecal matters becomes a cause of intoxication by the absorption which it favors. Therefore, a certain number of symptoms which are of the same nature, though not as intense as those of diarrhea, are caused by constipation. In fact, in both instances there is cephalalgia, fatigue, nervous disturbances, and tumefaction of the liver. It is to be noted, however, that in constipation the matters accumulated in the intestine, being excessively hard, do not readily allow the transudation of the toxins they contain.

Constipation exerts curious effects upon the constitution of the blood. By causing coprostasis in animals, Vanni[1] noticed that the red corpuscles diminished in number and became less resistant to destructive agents.

Although constipation is generally well borne by healthy individuals, this is not the case in those who have received some traumatism, in confined women, and in persons upon whom laparotomy has

[1] Vanni. Sull' origin intestinale della chlorosi. Il Morgagni, 1893, p. 533.

been performed. In more than one such case febrile paroxysms have appeared which might well be suspected as symptoms of septicemia, but which have vanished with evacuation of the bowels simply by the administration of an enema.[1]

The old surgeons were not, therefore, wrong in preparing their patients, and intestinal antisepsis practised for a few days before abdominal operations renders real service.

Intestinal obstruction under all its forms—internal strangulation, invagination—presents the most striking picture of digestive auto-intoxication. The theory of reflex action cannot account for the clinical manifestations, and it has yielded to the toxic theory. In fact, Senator has shown that, by lavage of the stomach, it is possible to cause the momentary disappearance of the symptoms of obstruction and that, by repeating this procedure, a cure may be effected. This successful result has since been observed by several physicians, notably by Drs. Bouchard and Chantemesse.

Prof. Bouchard has emphasized the importance of gastric intoxications by the study of dilatation of the stomach. Without intoxication it was impossible to explain the various manifestations observed, especially the nervous symptoms which, in their mildest forms, are characterized by prostration and a feeling of exhaustion at the moment of wakening, and, in their graver expression, terminating in aphasia, vertigo, tetany, and coma. Fetid sweat, cutaneous eruptions, congestion of the liver, albuminuria, peptonuria, trophic disturbances, notably the nodes of the second phalanges, are likewise referable to the formation of poisons. A few authorities go further and believe the same process is responsible for the deeper alterations of the osseous system, osteomalacia in adults, and, according to Dr. Comby, rachitis in children.

Poorly digested substances are easily attacked by microbes in the stomach and intestine. When, however, digestive disturbance is attended by hyperchlorhydria, extremely toxic substances are produced in the stomach which are responsible for dyspeptic tetany and coma. The question has been very carefully studied by Kulneff, Bouveret, and Devic, but it is still unknown what part is to be attributed to microbes in the genesis of these poisons and of ethyldiacetic acid. This acid has been credited with an important rôle in the pathogenesis of comatose phenomena, analogous to those produced

[1] Kustner. Zur Kritik der Beziehungen zwischen Faecalstase und Fieber. Zeitschr. für klin. Med., 1882, Bd. v.

by diabetes, which are observed in dyspepsias, dilatation, ulcer, or cancer of the stomach, and after the ingestion of tainted meat.

The experiments of Dr. Boix[1] demonstrate that butyric acid is capable of inducing atrophic cirrhosis; lactic and valeric acids exert a similar, though less intense, action; acetic acid is the most harmful, for it is sclerogenous and, at the same time, produces cellular degenerations.

Here is a series of facts which conclusively establish that secretory disturbances and putrefactions of the alimentary canal give rise to a great number of noxious products which are capable of causing immediate accidents or, in the long run, induce visceral lesions.

Finally, it is well to remark that in cases of nephritis, hepatic affections, cardiopathies, morphinomania, tuberculosis, and evidently also in typhoid fever and cholera, there are profound alterations in the stomach and intestine, and, consequently, putrid fermentations are produced, the effects of which are added to those of the primary disease.

The Toxins of the Pathogenic Microbes.

Multiplicity of Microbic Toxins. The idea of attributing the development of infectious diseases to intoxication is very old. In the presence of bacteriology it seemed for a moment to have lost ground. Soon, however, the first experimenters themselves began to suspect that microbes are not everything, and that toxins secreted by them played a rôle of prime importance. Diligent and methodic researches were undertaken on every hand and a great number of toxic bases of microbic origin were described.

Most of these bases do not contain oxygen, and, like the analogous alkaloids found in highly organized plants, they are not crystallizable. They are oily, colorless substances, with a cadaveric odor, seldom with an agreeable one. They are soluble in alcohol, ether, and all the usual solvents of alkaloids, and, like them, form salts which crystallize. Other less numerous bases are oxygenated and consequently crystallizable.

These results seemed to demonstrate the analogy between bacterial and vegetable alkaloids. Soon, however, objections were raised. It was pointed out that the ptomains extracted from cultures were far from possessing the same toxic potency as the total culture, and did

[1] Boix. Le foie des dyspeptiques. Thèse de Paris, 1894.

not produce the same phenomena. It was recognized that, as in the case of putrid poisons, the substances soluble in alcohol are not the most active, but, on the contrary, those precipitated by this liquid.

It seems certain that the bacterial poisons are very complex and, consequently, very unstable. They are, therefore, easily decomposed in the course of chemical manipulations, and what is obtained at the end of the researches is not the primary poison, but one derived therefrom. The toxalbumins, for instance, probably contain an alkaloidal nucleus which is separated from them on the slightest occasion. Therefore, one can never be sure of having obtained the primary body. Although methods of investigation have been multiplied, no absolutely reliable method has been found.

In view of the uncertainty of methods, it is well to precisely determine the initial toxicity of the sterilized culture. The active substances are subsequently separated without overlooking the fact that all reagents, including alcohol, which is so frequently employed, may decompose the toxic molecule. By combining the methods the conviction is reached that the majority of microbic poisons are precipitated by alcohol and adhere to the precipitates which form the various mineral salts in the culture fluid. This is, for instance, what occurs with aluminum hydrate and calcium phosphate. In view of these chemical results and of the fact that minute amounts produce violent results, toxins have been considered as ferments. Recently, however, under the influence of the researches of Brieger and Fraenkel, they have been designated by the vague term toxalbumins, and at times they are classed with nucleo-albumins. It is to be remembered that certain microbic poisons possess characters comparable to those of albumoses and peptones. Hence, the names toxalbumoses and toxopeptones applied to them.

In spite of the divergencies of detail, a fact is manifest, viz., that the toxins are complex molecules possessing certain characters of a ferment. Like the latter body, they are very unstable, adhere to various precipitates, and are altered and decomposed by heat and light. Like ferments and albumins, they are precipitated by alcohol, and are only slightly or slowly dializable. They may, therefore, be considered as proteid substances. "They are," says Prof. Gautier, "complicated ptomains."

It has been asked whether the question was rendered any clearer by comparing toxins to ferments—*i. e.*, to substances the nature of which is unknown and which reveal themselves by their functions

alone. A ferment is a complex substance which has received from living substance a certain degree of vital activity. It is, as Buchner states, "a semiliving matter." At all events, it is the highest expression of lifeless matter. Under these conditions the action of toxins is no more mysterious than that of ordinary ferments. The objection which consists in excluding toxins from this group because they do not hydrate albumin and do not act upon sugar is of little value. This is like asserting that pepsin is not a ferment because it does not convert starch into sugar. The microbic cell, like the animal cell, possesses different ferments; in other words, it is apt to transmit different forms of energy to different molecules.

In brief, bacterial poisons are complex and recognize several origins. The protoplasm of parasites contains proteins which have been well studied by Buchner. The culture fluid contains poisons which are formed by secretion or by synthesis and belong to the group of albuminoids. Besides those already referred to, there is one more toxin to be mentioned, namely, mucin, which is encountered in the cultures of various microbes, notably that of the tubercle bacillus (Weyl).

Action of Toxins upon the Organism. The effects produced by microbic toxins vary evidently according to the pathogenic agent under consideration. However, the symptoms observed may be divided into three groups. Some are produced at the point of introduction of the active substance and constitute the local lesions. Others express the impregnation of the entire economy, and are general manifestations. Lastly, there are symptoms indicating a selective action of the toxin upon some organ, apparatus, or tissue.

The local lesions are not constant. When any exist they vary, even for the same toxin, according to the activity of the latter, the point of introduction, and the amount of substance employed. The researches which I have pursued with the diphtheria toxin resulted as follows: When injected beneath the skin it produces, as is known, a very marked edema. When spread upon a mucous membrane exposed to the air, it gives rise to the formation of false membranes. If, however, it is very active or the animal is highly sensitive to its action, no local lesion is produced, but there occurs a general intoxication which rapidly ends in death.

Toxins also give rise to general disturbances. These are the only symptoms observed when the poison is introduced directly into the veins. No matter what the mode of introduction may be, or what

amount is introduced, the symptoms are never manifested instantaneously. Contrary to what occurs immediately after an alkaloid is injected, in most microbic intoxications there is a period of latency which lasts from a few hours to a day or two. The most important general manifestation is fever, which is accompanied by other phenomena: urinary disorders, secretory modifications, exchanges of gases, etc.

When the toxin is absorbed or when it is injected directly into the blood it may produce in the viscera a series of accidents varying with the poison and the animal. They consist in functional disturbances or in lesions, notably cellular degenerations. It is conceivable therefore, that if immediate death is avoided the intoxicated animal may later succumb to a progressive cachexia which is sufficiently accounted for by the numerous visceral alterations discovered at the necropsy. In other instances, an organ having been more particularly affected, some organic affection—chronic nephritis, myocarditis, cirrhosis, or myelitis—is developed, which pursues its own independent course.

Description of Principal Toxins. Among infectious diseases there is a group the pathological physiology of which is incomprehensible if the action of a toxin is not admitted. I refer to those maladies the pathogenic agent of which remains localized at the point of introduction, viz., diphtheria, tetanus, cholera, gaseous gangrene, and symptomatic anthrax.

The diphtheria toxin, discovered by Roux and Yersen, may be very active, its energy not being necessarily related to the pathogenic power of the culture. A very virulent bacillus is not necessarily very toxinogenous. An active toxin is that which kills a guinea-pig of an average weight in a dose of 0.1 c.cm. With the bouillon of Martin, 0.002 c.cm. suffices to kill a guinea-pig weighing 500 grams. If we remember that one cubic centimetre of the fluid gives one centigram of dry residue, say 0.0004 of organic matter, and that the toxin represents only one part of this organic matter, we can conceive the prodigious activity of the diphtheritic poison. An ordinary diphtheria toxin is sufficient to poison a weight of living being 20,000,000 times greater than its own.

Among the chemical substances which diminish the energy of this toxin are lactic, acetic, and tartaric acids. However, by again neutralizing the medium, we may in great part at least renew the toxicity. Oxidizing bodies, such as potassium permanganate, neu-

tralize its effects. The reducing substances, such as sulphuretted hydrogen, are indifferent. Iodine trichloride and iodin-water weaken the action of the toxin and permit its employment as a vaccine.

All animals are not equally sensitive to the diphtheritic poison, and those which are refractory to the living bacillus are so to the toxin. The guinea-pig is readily poisoned by it; the rabbit is less susceptible, and the dog still less. The mouse and the rat endure high doses.

Subcutaneous injection produces a local edema, which is often very marked, and congestion of the corresponding ganglia. In the rabbit it is followed by the formation of pseudomembranes, often very extensive and thick, occupying the larynx, trachea, and at times the intrapulmonary bronchial tubes. Upon the exposed mucous membranes the lesion remains local. When introduced into the alimentary canal, this toxin produces no effects.

Subcutaneous or intravenous injection of the toxin is not followed by any immediate symptoms. At the end of a period which varies with the activity of the poison and the quantity introduced, the guinea-pigs become cold and are seen to stay in a corner of their cage; they subsequently fall into a somnolent state and die in hypothermia. Rabbits frequently suffer from diarrhea. At the necropsy pulmonary congestion and edema, pleural effusion, congestion, and at times hemorrhages into the suprarenal capsules are found in the guinea-pig. In the rabbit the dominant changes are intense congestion of the liver and kidneys, with fatty degeneration of the cells, while the suprarenal capsules are generally intact.

When very small doses are injected, paralytic phenomena, especially in the rabbit, may be observed during life. At the necropsy alterations of the nervous system are frequently discovered. It is also in such cases that myocarditis is found, which has been well studied by Mollard, Regaud, and others.

The Tetanic Toxin. In the early studies of tetanus experimenters resorted, as is commonly the case, to complex methods, which subsequently were replaced by simpler procedures. Brieger, who was the first to investigate the poison of tetanus, endeavored to obtain chemically defined bodies. By experimenting upon the arm of a man suffering from tetanus, and upon impure cultures, he obtained, apart from the putrefactive bases already known, four new bases: tetanin, whose chemical composition is established by him to be $C_{13}H_{30}N_2O_4$, and causes trismus and then generalized tetanus in the mouse;

tetanotoxin, which produces convulsions or paralyses; spasmotoxin, which gives rise to clonic and tonic spasms; lastly, a base which stimulates the salivary and lacrymal secretions.

Kitasato and Weyl, experimenting with pure cultures, detected tetanin and traces of tetanotoxin, but these bases act only in enormous doses. As a matter of fact, the true poison is of a different nature, as has been demonstrated perfectly by Kund Faber. This author simply filters the culture fluid through porcelain and obtains a toxin resembling diastases, which is destroyed by alcohol or a temperature of 149° F. (65° C.). Injected into animals, it produces tetanus after a period of incubation. It behaves, therefore, like the diphtheritic toxin.

At present it is known that the tetanic poison is more of an albuminoid nature than a ptomain. Obtained by filtration of cultures, the poison is of such strength that $\frac{1}{100000}$ c.cm. suffices to kill a mouse. Dr. Nicolas, having accidentally pricked his own skin with the point of a needle charged with the toxin, was taken sick, after four days, with tetanus which proved to be of a benign character.

Two theories have been advanced with regard to the pathological physiology of tetanus: one, originated by Autokeatow and developed by Courmont and Doyon, admits an action of the poison upon the sensory nerves; the other, defended by Bruner, assumes increased excitability of the nerve centres—*i. e.*, a modification analogous to that produced by strychnine.

The Cholera Toxin. The choleraic poison was first studied by Petri, who considered it as a toxopeptone, and by Hueppe and Scholl, who cultivated the vibrio in egg albumin without being able to completely remove from their preparations of toxin sulphuretted hydrogen and alcohol (Gruber and Wiener).

The question has further been studied by Westbroock, who obtained a hypothermizing poison; by Sanarelli, who isolated a toxin acting through the alimentary canal; by Brieger and Fraenkel, who prepared an unstable protein. The most important contributions have come from Pfeiffer and Ransom. The results are, however, contradictory. Pfeiffer asserts that the poison resides in the body of the microbe, while Ransom contends that the toxin is a soluble substance which resists a temperature of 212° F. (100° C.) and, in small doses, causes death in collapse; in high doses, its action is instantaneous.

The question was taken up and completely studied by Drs. Metchnikoff, Roux, and Taurelli-Salimbeni. These authorities began by exalting the vibrio by means of a very ingenious procedure, which consists in cultivating it in small capsules of collodion introduced into the peritoneum of guinea-pigs. When the microbe has become quite energetic, it is transferred to a fluid containing 2 per cent. of gelatin, 2 per cent. of peptone, and 1 per cent. of sea salt. The most active poison is obtained on the third or fourth day. A dose of 0.3 c.cm. per 100 grams kills a guinea-pig in sixteen to twenty-four hours. This poison differs from the cholera and diphtheria toxins in that it resists boiling. It is destroyed by sunlight, precipitates ammonium sulphate and strong alcohol. Injected into guinea-pigs, it produces prostration, meteorism, and diarrhea. The animals succumb in hypothermia.

Toxins of Gaseous Gangrene and Symptomatic Anthrax. The bacilli of gaseous gangrene and of symptomatic anthrax are two very closely related anaërobics. They resemble the preceding microbes in their tendency to remain localized, although they invade the organism more easily, at least when the question is one of small laboratory animals.

The poison of gaseous gangrene, studied by Roux and Chamberland, and more completely by Besson, when injected in a dose of 3 c.cm. to 5 c.cm. into the peritoneal cavity of guinea-pigs weighing from 450 to 600 grams produces grave symptoms with hypothermia. The animals recover, however. Introduced subcutaneously, the poison gives rise to considerable edema and at times to an eschar. The latter result is of great interest, since it elucidates the mechanism of gangrenous lesions. To kill a guinea-pig of 300 to 400 grams, the injection of 5 c.cm. to 10 c.cm. is required.

It is not easy to state whether the poison of gaseous gangrene is identical with or analogous to that of symptomatic anthrax, since researches have not been pursued under altogether similar conditions.

The Toxin of Anthrax. We now come to that group of microbes which manifest a tendency to invade the entire organism. The list may properly be headed by the *bacillus anthracis* and the microbe of *chicken cholera.*

The preparation of the anthrax toxin seems to be quite difficult, and its study has been the subject of numerous contradictory researches. The poison seems to remain long enclosed in the bacterial

cellule. It diffuses tardily and only in media prepared in a special manner.

The best work on this subject is due to Marmier. This author cultivated the bacillus in a medium containing 40 per cent. of peptone and 4 per cent. of glycerin. The active substance is extracted by means of ammonium sulphate and alcohol. If the culture has been kept at 96.8° F. (36° C.), the toxin is slight in amount; it is abundant if the medium has been kept at 68° F. (20° C.) for a fortnight. This toxin, injected into animals, causes a fever which is ushered in toward the fourth hour, and reaches its maximum the following day. Diarrhea makes its appearance, the animals become thin, cachectic, and, after convulsions, succumb in hypothermia.

Toxins of the Bacilli of Hemorrhagic Septicemias. Some researches have been made on various agents of hemorrhagic septicemias, notably those of hog cholera. De Schweinitz found albuminoids (sucholealbumins) and a ptomain (sucholetoxin) toxic for the guinea-pig. Novy isolated a toxalbumin and a protein. Voges[1] has also done important work bearing on this subject. His conclusion is, with regard to the toxins, that the poison is contained in the microbic cells. This is proved by treating the cultures with chloroform, carbolic acid, or tricresol. Subjection to a temperature of 122° F. (50° C.) or 140° F. (60° C.) or to ebullition for ten minutes likewise yields good results. Absolute alcohol exerts a very marked destructive action upon the toxin.

Among the septicemic agents observed in man, *proteus vulgaris* may be mentioned. Its sterilized cultures are almost as active as the living cultures and produce about the same general as well as local effects. According to Foa and Bonome, the chief toxin is nervin, which is abundantly present in the cultures.

Toxins of the Bacillus Septicus Putidus. The soluble products of the *B. septicus putidus* are very active. Half a cubic centimetre is sufficient to kill one kilogram of rabbit within five to fourteen days. A dose of 20 c.cm. to 30 c.cm. kills in a few hours, and 45 c.cm. proves fatal in a few minutes. In such acute cases there is paresis and convulsions, death supervening by arrest of respiration.

The Pyocyaneus Toxin. Like the preceding, this bacillus may be observed in man, but its chief interest is due to the experimental

[1] O. Voges. Kritische Studium und exp. Untersuchungen über die Bakterien der hamorrhägischen Septikämie und die durch sie bewirkter Krankheitsformen. Zeitschr. für Hygiene und Infektionskrankheiten, 1896, Bd. xxiii.

researches to which it has been subjected. Everyone is aware of the interesting work of Charrin, who was able, with sterilized cultures, to produce in animals symptoms identical to those caused by the microbe itself.

The Toxins of Colon Bacillus. On account of the important rôle which the colon bacillus plays in the organism, even under normal conditions, it is proper to give it special attention in this cursory review.

The soluble products secreted by this microbe, or rather by the various bacteria constituting the group of colon bacilli, have been well studied by Denys and Brion, and particularly by Gilbert.[1] From these researches it is shown that the toxins of the colon bacillus are of varying potency according to the virulence of the germ; moreover, they are the more powerful the older the culture. Nevertheless, to cause death, Gilbert had to inject very large doses, varying from 37 c.cm. to 74 c.cm. per kilogram of animal.

Rabbits which receive the sterilized culture become weak and the muscles manifest fibrillary trembling. Convulsions and nystagmus then supervene. The third stage is characterized by a violent tetanus, to which the animal succumbs. The nervous phenomena depend upon spinal changes easily discoverable in frogs.[2] The intoxication in this animal is comprised in three stages: a stage of initial paresis, a stage of muscular hyperexcitability, and a stage of paralysis. The tracings which I have obtained clearly show that the poison acts upon the spinal cord and, secondarily, upon the muscles.

The poison of the colon bacillus, the effects of which have just been referred to, is constantly produced in the intestine. A part of it is arrested and transformed by the intestinal epithelium, as was demonstrated by Denys; another part penetrates the organism. However, since absorption is effected by the portal vein, the liver may exercise a protective rôle, and, as a matter of fact, we have established that this gland is capable of arresting and transforming the intestinal poisons. That portion escaping the action of the liver is eliminated by the urine and contributes to the toxicity which this secretion presents under normal conditions. Gilbert justly remarks that certain symptoms are common to intoxications produced either by the

[1] Gilbert. Des poisons produits par le bacille intestinal d'Escherich. Soc. de biologie, February 25, 1893, p. 214.

[2] Roger. Etude sur la toxicité des produits solubles du B. coli communis. Arch. de physiol., July 1, 1893.

urine or by the colon bacillus, and that, moreover, when putrefactions of the intestine are checked by antiseptics, the toxicity of the urine is at the same time reduced.

Under various pathological conditions the virulence of the colon bacillus increases. In some instances, the microbe invades the organism and produces therein the soluble substances the effects of which have just been referred to. These effects are more pronounced when the protective organs of the economy are more or less altered by the disease.

The author made an experimental study of the toxins produced by a colon bacillus representing the cause of a variety of dysentery.[1]

The cultures of this colon bacillus inoculated into rabbits proved extremely virulent. A few drops injected into a vein caused death in less than a day, at times in six hours. This microbe produced very strong toxins in the culture media. When the culture medium was composed of equal parts of bouillon and serum, instead of simple bouillon, the results were more interesting. At the end of eight days the culture was sterilized by means of chloroform, which was subsequently removed by decantation and evaporation. The fluid thus prepared was so very toxic that ten drops injected into the veins of a rabbit of 2 kilograms sufficed to produce fever, diarrhea, and, finally, death in twenty-four or forty-eight hours. With a second sample, furnished by a bacillus exalted by passages through animals, 18 c.cm to 20 c.cm. caused death within an hour or two.

One of the first symptoms produced by the toxin is diarrhea, which is at times extremely profuse, amounting to a continuous evacuation. Hence the rapid loss of weight suffered by the animals. The toxin prepared with the exalted microbe exerted a far more energetic action, but gave rise to very little, if any, diarrhea. It may, therefore, be admitted that the intestinal flux eliminates not only the poisons originated in the digestive canal, but also the noxious substances which may have penetrated the economy.

The Toxins of the Pyogenic Microbes. The pus cocci constitute a group, at the head of which we would place the staphylococcus. The staphylococcic toxin is of considerable interest with reference to the study of suppuration. It will be treated in the chapter devoted to this question. The poison may likewise give rise to general mani-

[1] Roger. Les toxines du colibacille de la dysenterie. Ann. de la soc. de méd. de Gand, 1900, p. 139. Le colibacille de la dysenterie. Presse méd., July 4, 1900.

festations. In this respect, however, its history is not so important as that of the streptococcus.

The study of the soluble products of the streptococcus was first made by Manfredi and Traversa. In a highly remarkable memoire these authors have shown that the cultures of this microbe, freed from all figurate elements by means of porcelain filters, are toxic for the frog, guinea-pig, and rabbit. In the last-named animal, thirty to fifty minutes after subcutaneous injection of the filtered fluid, a certain degree of somnolence is observed, then a slight paresis of the extremities. In most cases the animal recovers in a few days.

To obtain the toxic substances, the author[1] cultivated the streptococcus in thick bouillon protected from the air by a layer of oil. The fluid was filtered at the end of fifteen days and injected into the veins of a certain number of rabbits. The fatal dose, which varied somewhat from one culture to another, oscillated generally between 13 c.cm. and 20 c.cm. per kilogram. After the injection the animals remained in a state of somnolence; the next day they presented a very profuse diarrhea. Death supervened at the end of two or three days.

To establish the nature of the toxin the filtered fluid was treated with ten times its volume of absolute alcohol. The resulting abundant precipitate was washed with alcohol and redissolved in a 7 per 1000 salt solution. The alcoholic fluids were united and evaporated at a low temperature. The residue was then treated with salt water. Two extracts were thus obtained which were studied separately. The alcoholic extract did not prove to be toxic. On the other hand, the aqueous extract gave rise to the same disturbances as the total culture, except that higher doses were required.

The toxin of the streptococcus when submitted to a temperature of 219.2° F. (104° C.) is considerably weakened. This is true of the total culture as well as of the aqueous extract.

The Toxin of the Pneumococcus. The toxin of the pneumococcus, which has been prepared and well studied by Drs. Carnot and Fournier, is so active that a few drops of it injected into the lung produce a focus of pneumonia characterized by flatness, crepitant râles, and bronchial breathing. At the necropsy, fibrinous pneumonia, comparable to that observed in man, is discovered. By varying the

[1] Roger. Action des produits solubles du streptocoque de l'érysipèle. Soc. de biologie, July 4, 1891. Contribution a l'étude expérimentale du streptocoque de l'érysipèle. Revue de méd., December, 1892.

experimental conditions, other varieties of pulmonary lesions may be produced, such as hemorrhagic pneumonia, gray hepatization, and abscess of the lung.

The Toxin of Typhoid Fever. The typhoid toxin has been studied by Brieger and Fraenkel, who believed it to be a toxalbumin. Sanarelli experimented with extracts obtained by macerating the bacilli for six months. The toxin thus prepared produces hypothermia, abdominal meteorism, mucous and sanguinolent stools. Death occurs in coma.

According to Chantemesse and Ramond, the toxin is rapidly destroyed in the cultures by oxidation. These authors employ as a medium a bouillon prepared with spleen digested by fresh pepsin derived from the stomach of a pig. The poison manifests the greatest energy on the fifth or sixth day. It is very active for the guinea-pig, rabbit, sheep, dog, and especially the horse. If the amount injected into a rabbit is very small, hyperthermia is the result; if it is large, then hypothermia occurs. At the same time diarrhea makes its appearance, followed by respiratory and circulatory disturbances. The necropsy reveals congestion of the intestine and abdominal organs, liver, kidneys, and spleen. In his more recent researches, Chantemesse made a very minute analysis of the action exerted by this toxin upon the heart and nervous system.

Toxins of Glanders. We shall mention one more toxin, that of glanders, which, according to Finger, produces rapid death, or, if the dose is less strong, a progressive cachexia accompanied by paralytic manifestations. Babès and Motoc isolated from the cultures a substance insoluble in alcohol and possessing a very marked thermogenic action. Its injection produces spasms, and, if the injections are repeated, nephritis results, and death supervenes in marasmus.

Poisons Found in Infected Organisms. Aside from the poisons due to the microbe, the diseased organism itself elaborates some. These may be divided into three groups:

1. Poisons produced by the organism under the influence of pathogenic microbes. This group includes poisons which cannot originate in culture media, the microbes attacking the constituent elements of the invaded organism directly or through the ferments which they secrete.

2. Poisons derived from the alimentary canal in the course of infections, in which putrefaction is always increased.

3. Poisons derived from disassimilation, which is increased and

perverted. To this cause are probably due the profound modifications occurring in the chemical constitution of the organism in the course of febrile maladies. The alkalinity of the blood is diminished: instead of representing 4 to 5 grains (238 to 280 milligrams) of soda, it corresponds to no more than about three-fourths of a grain (40 milligrams), the change being due to the increase of acids, notably formic, acetic, diacetic, β-oxybutyric, and lactic acids, and volatile fatty acids.

The increased acidity results in increased elimination of ammonia. The extractive material and amidate bodies increase at the same time. The nutritive disturbances engendered by infections are also expressed by other modifications in the excretion of nitrogenous bodies—*i. e.*, serinuria, globulinuria, albumosuria, and probably acetonuria. To these should be added toxalbumins, which were detected by Alt in the vomitus of choleraic patients, and by Brieger and Wassermann in the urine of an erysipelatous subject.

Toxicity of the Blood and Urine in Some Infections. The toxicity of the blood may be increased in very notable degree. Very grave accidents and death are the results when 10 c.cm. to 15 c.cm. of the serum of a rabbit suffering from anthrax is injected into a healthy rabbit. Bose demonstrated that the serum of cholera-stricken patients injected into rabbits, in the proportion of 3 c.cm. to 5 c.cm. per kilogram, causes death within twelve to sixteen hours with choleriform symptoms.

The toxic substances have most often been sought for in the urine. Some have been content to study its total toxicity; others have endeavored to isolate from the urine some definite substance; in most cases a ptomain. In 1882 Prof. Bouchard detected in the urine of typhoid patients the presence of alkaloids, of which he obtained as much as one milligram a day. Two years later Drs. Lépine and Guérin made the same observation in cases of typhoid fever and of pneumonia. Dr. Lépine further recognized, with Dr. Aubert, that the toxic substances of organic nature are considerably increased in febrile urine, while mineral poisons suffer no variation.

The second method consists in studying the toxicity of the urine without reference to the nature of the poison to which it is due. It is by this procedure that Prof. Bouchard revealed the special properties possessed by the urine of cholera patients. It may be stated, without exaggeration, that his work is the fundamental study on this subject, and has been taken as a model for further researches.

Dr. Lépine discovered a toxic alkaloid in the urine of pneumonia patients. The amount of the alkaloid increases in proportion to the intensity of the disease and possesses the power to arrest the heart in diastole. The presence of alkaloids in the urine of pneumonia cases has been confirmed by the researches of Griffiths and Albu.

Researches pursued with Dr. Gaume[1] showed us, contrary to all expectation, that the toxicity of the urine diminishes as the disease progresses. At the end of the stationary stage the toxicity is often no more than half or one-third of the normal. Later, at the moment of defervescence, a urotoxic crisis occurs, and the toxicity again rises above the normal. In some instances it exceeds but slightly the normal toxicity; in others it acquires a double, treble, or even quadruple value. This excessive toxicity lasts twenty-four to forty-eight hours. During convalescence the urine presents a variable toxicity, which may be equal to, below, or above the normal.

Similar researches have been made by various experimenters upon the toxicity of the urine in erysipelas, variola, scarlatina, typhoid fever, tetanus, malaria, influenza, tuberculosis, and leprosy. It is curious to note that, in most cases, the poison detected in patients is of alkaloidal nature, while the microbic poisons, as discovered in artificial cultures, belong to the category of albuminoids and peptones. This lack of harmony is, perhaps, due to the fact that the poisons are multifarious and that substances other than bases have not sufficiently been looked for. It is possible, however, that microbes act in the bodies of animals otherwise than in culture media. Finally, it may be supposed that the ptomains are produced by the organism itself reacting in a special manner under the new conditions imposed upon it. As a matter of fact, apparently insignificant changes suffice to completely modify the physiological action of organic compounds.

Griffiths has rightly remarked that a toxic base, propylglycocyamin, is found in the urine of patients suffering from various affections. This base is no other than creatin, an inoffensive substance, in which an atom of hydrogen has been replaced by the radical propyl. This simple change has resulted in a complete transformation in the physiological action. Klebs has reported a similar example. According to him, cholera nostras is dependent upon methylguanidin, a violent poison derived from guanidin, a harmless body, by substitution of a group of methyl for an atom of hydrogen.

[1] Roger et Gaume. Toxicité de l'éurine dans la pneumonie. Revue de méd., 1889.

It is conceivable that, in the same disease, according to a variety of secondary circumstances, autointoxication may be due to various substances. The results of researches have, therefore, not always agreed. The toxicity of the urine varies from one patient to another. In two individuals suffering from the same disease the urine of one may contain alkaloids, while that of the other may be free from them.

Aside from the poisons secreted by the microbes or produced under their influence, there are also those arising from lack of oxidation in the course of various affections. This point has been well established by the researches of Dr. Albert Robin. As a result of the insufficient transformation of toxic substances in the more or less disturbed organs, poisons reach the kidneys in excessive quantities. If these emunctories are in a normal condition, the urine eliminates the noxious bodies; if not, they are accumulated in the economy to be thrown out at the time of crisis.

Rich and encouraging as are the results of researches touching the question of intoxications in infectious diseases, other facts of great interest are sure to be brought to light to clear up contradictions and obscurities.

CHAPTER V.

MICROBIC ASSOCIATIONS.

Experimental Demonstration of the Rôle of Microbic Associations. Association of Saprophytes with Anaërobic and Aërobic Microbes. Mechanism of Microbic Associations. Exposition and Criticism of Various Theories. Application of Experimental Data to Clinical Medicine. Simultaneous Evolution of Two Infections. Successive Infections. Secondary Infections. Combined Infections in the Skin, in the Nasobuccopharyngeal Cavity, in the Respiratory Apparatus, and the Alimentary Canal. Secondary Septicemias. Their Importance in the Course and in Consequence of Acute Infections. Secondary Infections in Chronic Diseases. Favorable Influence of Certain Secondary Infections.

Experimental Demonstration of the Role of Microbic Associations. The analysis of clinical facts had long demonstrated the frequency of microbic associations.[1] It had been established that, in a great number of cases, two or several bacteria simultaneously or successively invaded the organism. To better comprehend the signification of these clinical revelations it was necessary to transfer the question upon experimental ground and discover the effects produced by simultaneous inoculation of two different microbes, one pathogenic, the other inoffensive. This the author undertook to do in 1889.

The author first studied the results of association of the *B. prodigiosus* with an anaërobic microbe, namely, with a specimen of septic vibrio which was not pathogenic for the rabbit.[2] He next experimented with the bacillus of symptomatic anthrax.[3]

Considered as a simple saprophyte, the *B. prodigiosus* may be injected into the muscles of a rabbit without producing any notable disturbance. One or 2 c.cm. of a gelatin culture are well endured. While, however, this bacillus does not cause death, it does not seem to be altogether harmless.

[1] Héricourt. Les associations microbiennes. Revue de méd., 1887, p. 995.

[2] Roger. Quelques effets des associations microbiennes. Soc. de biologie, January 19, 1889.

[3] Roger. Inoculation du charbon symptomatique au lapin. First note, ibid., February 2, 1889. Second note, ibid., March 30, 1889. Des produits microbiens qui favorisent le développement des infections. Compte Rendu de l'Acad. des Sc., July 29, 1889. Contribution a l'étude expérimentale du charbon symptom. Rev. de méd., March 10 and June 10, 1891.

The second microbe which the author used, the bacillus of symptomatic anthrax, is an anaërobic bacillus possessing most of the characters of the septic vibrio, but no pathogenic power whatever for the rabbit. It rapidly kills the guinea-pig, producing in this animal the well-known lesions of gaseous gangrene. If the serous fluid of a guinea-pig thus infected is inoculated into a rabbit, no disturbance results. I have injected with impunity quantities varying from two to ten drops. Of fifteen rabbits thus treated, none succumbed.

Here, therefore, are two microbes which, even in considerable doses, give rise to no disturbance when inoculated into the rabbit.

When, however, one or two drops of the gangrenous serous exudate of the guinea-pig is mixed with 0.75 c.cm. or 1 c.cm. of a culture of the *B. prodigiosus*, and the mixture injected into the muscles of the thigh of a rabbit, this animal dies in less than twenty-four hours; at times in eight hours.

The necropsy reveals lesions absolutely characteristic and altogether similar to those observed in the guinea-pig.

The microbe which had proved fatal, owing to the association of the *B. prodigiosus*, had acquired a slight increase of virulence. The serous exudate reinoculated into a second rabbit caused the death of the latter, but the edema fluid of this second animal inoculated into a third produced no effect.

In a second series of researches the author employed as auxiliary agents other microbes than the *B. prodigiosus*. It is readily understood that the field of these experiments was limited, for the author could not employ those bacteria the inoculation of which was fatal to the animal. Hence, the pyogenic agents were chosen for the purposes of the research, and first the staphylococcus aureus, the most widely distributed of all. The specimen employed was derived from a furuncle, and was not very virulent. It was found necessary to inject 0.6 c.cm. of a completely liquefied gelatin culture with 0.02 c.cm. of symptomatic anthrax in order to overcome the resistance of the rabbit. When the same amount of staphylococcus was injected alone a large abscess was the result, which healed after spontaneous rupture.

The *bacillus proteus vulgaris* proved more active. The injection of 0.25 c.cm. of a liquefied gelatin culture sufficed for the development of symptomatic anthrax.

Finally, the pyogenic streptococcus was experimented with. In this case, however, the addition of 1 c.cm. of a bouillon culture to

0.02 c.cm. of symptomatic anthrax culture was followed by no symptoms.

It is hardly necessary to say that no absolute value should be placed upon these results. The action of the auxiliary microbe must vary with the specimen employed. However, the experiments above reported suffice to establish the synergic rôle of two microbes. In other words, it demonstrates that two bacteria which are harmless for the animal when taken separately, become pathogenic and rapidly produce death when they co-operate.

Microbic Products Favorable to Infection. Let us now endeavor to enter a little deeper in this research and point out the mechanism set at work by the auxiliary microbes in order to bring about the development of a virulent disease in an animal naturally immune.

To explain the action of auxiliary microbes two hypotheses may be advanced: (1) The microbes may be supposed to act as living elements by some mechanical action, or by appropriating nutritive substances and oxygen destined for the tissues, thus weakening the resistance of the latter. (2) It may be assumed that the microbes secrete chemical substances which locally alter the muscles or, being absorbed, disturb the general state of the invaded organism.

The idea that the auxiliary microbes act by soluble products is in harmony with the results obtained in various infections. The author, therefore, first attempted to verify the accuracy of this hypothesis. For this purpose it was evidently sufficient to inject into the muscles a mixture of symptomatic anthrax and a certain amount of a culture deprived of living microbes. To secure the latter the author sterilized the fluids by heat. By employing a culture of *B. prodigiosus* which was kept for ten minutes in the autoclave at a temperature of 219.2° F. (104° C.), he noticed that the fluid thus prepared acted like the living culture. It was only necessary to employ a little more of the sterilized culture, namely, 1 c.cm. to 1.5 c.cm. This partial weakening of the fluid was to be expected. Aside from the alterations which heat may produce in the active substance, account is to be taken of the products secreted by the living microbe when developing the muscular tissue.

Similar results were obtained with sterilized cultures of *proteus* and of staphylococcus. It was found necessary to employ, on an average, 0.5 c.cm. of the former and 1 c.cm. of the latter.

The immunity of the rabbit from symptomatic anthrax may be

strengthened by injecting into its veins a few drops of anthrax serous exudate. As soon as this is done the animal becomes refractory against the microbic association. Rabbits which had received two injections at an interval of eight days were inoculated a week after with the two microbes. They resisted perfectly. A few of them presented only a local lesion. The thigh became edematous; then, a few days later, the swelling subsided. In a certain number of cases an abscess was formed which soon healed spontaneously.

The author then made an attempt to vaccinate the animals against the effects of the microbic association by previously inoculating them with the other microbe—*i. e.*, the *B. prodigiosus*. Living or sterilized cultures were repeatedly injected beneath the skin or into the veins. The results were always negative in so far as the animals died when they were subsequently inoculated with the two microbes.

These various results prove to what extent the experimenter is able to vary morbid aptitudes. The rabbit is by nature immune from symptomatic anthrax. If, along with the virus, the soluble substances secreted by another microbe be introduced, the disease is surely contracted. If, however, an intravenous injection of anthrax virus is previously made so as to reinforce the natural immunity, the animal is protected against the effects of the microbic association.

The rabbit is not the only animal whose immunity may be overcome by means of microbic associations. The results, as experiments have shown the author, are similar when the pigeon is operated upon, which is also, as is known, refractory to symptomatic anthrax.

Examples of Microbic Associations. The bacillus of symptomatic anthrax is an anaërobic agent to which that of tetanus may naturally be compared. Therefore, the study of microbic associations might well be resumed with this microbe. That is what Drs. Vaillard, Vincent, and Rouget have done.[1]

Experimenters first recognized that cultures of the tetanus bacillus injected into an animal not very sensitive to this infection—viz., the rabbit—produces a fatal disease if a small amount of *B. prodigiosus* is at the same time introduced. Extending experimental analysis further, investigators established that the spores of tetanus are incapable of germinating in a living organism or of giving rise to the

[1] Vaillard et Vincent. Contribution a l'étude du tetanos. Ann. de l'Inst. Pasteur, January, 1891. Vaillard et Rouget, Contribution a l'étude du tétanos. Ibid., June, 1892. Note au sujet de l'étiologie du tétanos. Ibid., November, 1893.

slightest disturbance. The culture produces symptoms because of the soluble products contained in it, and not by virtue of the figurate elements. The soluble substances act rapidly and induce a fatal intoxication. If care is taken to wash all toxic products from the spores, their injection produces no effect. If, however, a small amount of a living culture of *B. prodigiosus* is injected at the same time, tetanus develops. Under natural conditions the phenomena are analogous: the tetanus spores enter contused tissues or penetrate along with common bacteria, which promote their development. All microbes, however, are not capable of playing the part of an auxiliary. The bacillus of Friedlaender, the staphylococcus aureus, the streptococcus, and *B. subtilis* have remained without effect.

Since the first publication of the researches on microbic associations the question has been pursued by a very great number of experimenters, among whom may especially be mentioned Blachstein, Zumpf, and Metchnikoff, on microbic associations in cholera; Sanarelli on the rôle of the colon bacillus in the development of typhoid infection; Mosny on the influence of the soluble products of staphylococcus in the production of pneumonia, and Feltz, who demonstrated that the toxins of the colon bacillus increase the virulence of the *bacillus anthracis* and of the *staphylococcus aureus*.

Favorable Influence of Certain Microbic Associations. Although in the majority of cases microbic associations considerably aggravate the prognosis of infections, the reverse may also be observed. One microbe may hinder the evolution of another, and the organism finds an unexpected ally in one of the two pathogenic agents.

The starting point of researches upon this subject was the work of Emmerich, who declared that guinea-pigs which had resisted an inoculation of streptococcus became refractory to anthrax. Six hours after subcutaneous injection into a guinea-pig thus prepared the anthrax bacteria were altered. At the end of twelve or seventeen hours they were destroyed.

Taking up this research, Pawlowsky noticed that previous or simultaneous inoculations of either pneumobacillus, streptococcus, or, particularly, staphylococcus, arrested the development of anthrax. While, however, these microbes confer immunity against subcutaneous inoculations of anthrax, they are far less powerful against intravenous inoculations. By injecting two microbes, one after the other, into the veins, death may be delayed, but the animals are not saved. These interesting facts have been confirmed by further

researches. In the experiments of Pavone guinea-pigs which had previously been injected with typhoid bacilli resisted anthrax infection.

To explain the mode of action of microbes which prevent infection the theory of antagonism of bacteria has been proposed.

Pasteur had long recognized the importance of studying the development of two or more microbes in the same medium. In 1887 he pointed out that the *bacillus anthracis* hardly develops in a bouillon which has been used for the culture of the bacillus of chicken cholera.

These observations, however, were not conclusive. Garré was one of the first to undertake systematic researches upon this interesting question. He discovered that culture media which are exhausted by the vegetation of a microbe are unfit for the development of other bacteria. The exactness of this result has been recognized by various experimenters. On the other hand, it has long been known that when various microbes are cultivated in the same medium, a sort of struggle for existence takes place among them. Some die; others survive. If successive cultures are made, the same competition occurs, and finally, only one species remains in the culture. This is an instance of true natural selection. The most resistant species is, as a rule, the one most widely distributed and the least pathogenic. Such, however, is not always the case. One bacterium may favor the development of another. An aërobic microbe, by appropriating the oxygen, may aid the multiplication of an anaërobic bacterium. When, however, associated vegetation is possible, modifications in the chromogenic, toxicogenic, and pathogenic functions may occur. The toxin of tetanus, for instance, increases the virulence of certain pathogenic microbes (Roncali, Klein). The streptococcus causes the diphtheria bacillus to secrete a greater amount of toxin (von Schreider).

Mechanism of Microbic Associations; Exposition and Criticism of Different Theories. Do the various results above described enlighten us as to the key of microbic associations? Can it be assumed, for instance, that a microbe hinders or favors an infection because it produces substances which are harmful or favorable to the pathogenic agent? This doctrine has been advocated by some, but it seems to me unacceptable. It is contradicted by the results obtained by studying the association of sterilized cultures of *B. prodigiosus* with *bacillus anthracis* or with the bacillus of symptomatic anthrax. By injecting beneath the skin of the ear of a rabbit

a mixture of 0.01 c.cm. of a culture of *bacillus anthracis* and 0.5 c.cm. of a culture of the *B. prodigiosus* sterilized at 230° F. (110° C.), a local lesion characterized by swelling, redness, and heat, occurs. The control animals inoculated with pure anthrax present a little edema without redness or heat, and succumb from the second to the fifth day. The others survive the inoculation and die later than the controls.[1]

The resisting animals have not become immune. They die when they are subsequently reinoculated beneath the skin of the ear. A special phenomenon only is produced, namely, an enormous edema, invading the eyes, the cheeks, the forehead, and giving a very strange aspect to the face.

If the same experiments are repeated upon guinea-pigs, diametrically contrary results are obtained. The animals which receive the mixture of anthrax and *B. prodigiosus* present early and very extensive edemas and succumb several days before the controls. The differences are quite clear when cultures of low virulence, permitting a sufficiently long survival are employed. The effects are identical whether the *B. prodigiosus* be injected into the same point where the anthrax is or into a different region.

Reciprocally, Deuschmann has shown that the *B. prodigiosus*, which facilitates the development of symptomatic anthrax in the rabbit, exerts a contrary action upon the guinea-pig. While it abolishes the immunity of the refractory animal, it enables the animal which is naturally susceptible to resist a virulent inoculation.

These facts again demonstrate how hazardous it is to jump to generalizations. They are also of special interest because they serve to disprove all the theories offered in explanation of the mechanism of microbic associations.

These theories are already very numerous. They call to their aid either modifications of diapedesis or of phagocytosis, or an action of microbic toxins upon the pathogenic agent. According to Drs. Vaillard and Vincent, who have studied the adjuvant action of living cultures of the *B. prodigiosus* upon tetanus, the phagocytes are busy incorporating the saprophyte bacilli, and, while they are engaged in this easy pursuit, the tetanus bacillus has time to develop and to secrete its toxins. This view was no longer tenable after Drs. Vaillard and Rouget recognized that the soluble products acted like the virulent cultures. They then were led to modify their theory and

[1] Roger. Influence des produits solubles du B. prodigiosus sur l'infection charbonneuse. Soc. de biologie, May 10, 1895.

argue that the microbic products exert a chemiotactic action. These products possess the double property of attracting the leucocytes and of necrosing them.

According to Prof. Bouchard, the toxins act by influencing the vasomotor centres. According as they favor or hinder reflex vasodilatation, they favor or hinder diapedesis and phagocytosis and, consequently, assist the organism or, on the contrary, the microbe. Among others, the following objection is to be made against this theory: In order to paralyze the vasomotor centres, considerable quantities of toxin must be introduced; in order to produce infection the injection of a fraction of a drop suffices. What is, however, still more grave is the fact that this theory, as well as that of Vaillard, does not explain the variability of results obtained according to the species operated upon and the microbe employed. If the *B. prodigiosus* prevents phagocytosis when it is associated with tetanus or with symptomatic anthrax, why does it favor phagocytosis when it is combined with the *bacillus anthracis?*

If, on the contrary, it be admitted that microbic toxins act by modifying the germicidal power of the blood, it is plain that the supervening changes may inhibit one species of bacteria and favor the action of another. I recognize that my explication is no more than a hypothesis needing experimental control. However, it is supported by some facts. According to Nissen, the germicidal power of the blood is abolished when a sufficiently large amount of microbes is injected into the veins. Bastin, after confirming Nissen's discovery, obtained analogous results by employing cultures sterilized by means of heat, chloroform, or ether. He further established that there is a relationship between the dose injected and the degree of diminution of the germicidal power. Lastly, he has pointed out that when the germicidal power is abolished for one species, say for the staphylococcus aureus, it may be so with regard to another, the *B. lactis aërogenes*, for instance. If it is some day recognized that the germicidal power is increased for certain agents, the demonstration will be perfect. For the time being, however, the explanation presented by us is only an hypothesis, but it is the only one in accord with the results thus far obtained by experimentation.

Clinical Study—Combined Infections.

Clinical observation first led to experimental researches on microbic associations. In its turn, experimentation sheds light upon facts

observed in the sick and enables us to comprehend the mechanism of combined infections.

There are four orders of facts to be considered:

1. Two exogenous infections evolving simultaneously in the same subject.

2. Two infections evolving successively.

3. An acute infection attacks an individual who has previously suffered from a chronic infection.

4. An intercurrent infection favors the development of pathogenic germs which, until then, vegetated without any inconvenience upon the skin and mucous membranes. This last group is, perhaps, the most important of all.

Simultaneous Occurrence of Two Infections. When two infections develop simultaneously, they evolve side by side, each preserving its special characters. An aggravation in their evolution may sometimes be observed. Even then, however, the two processes remain distinct. Such is the case, for instance, when two eruptive fevers develop in the same individual. In most cases, measles and scarlatina coexist. The two eruptions may appear at the same time, each developing at points of the skin which have been spared by the other. Each disease behaves as if it were alone, except that, in many cases, the eruptions last for a shorter time than usual. The prognosis is in nowise modified.

We cannot dwell upon all possible combinations. Variola, scarlatina, vaccinia, typhoid fever, and whooping-cough may occur one with another. Measles may coexist with whooping-cough, typhoid fever with pneumonia, and, in hot countries, with malaria, and, though very seldom, even with tuberculosis.

In its various stages, syphilis may be associated with other infections. At the start it may be a "mixed chancre," resulting from the simultaneous inoculation of the syphilitic virus and that of soft chancre. In these cases, the soft chancre, the period of inoculation of which is shorter, appears first. A few days after its base becomes hard, then the soft chancre is healed while the syphilitic lesion persists. The chancre is, therefore, mixed but for the middle period of its existence. A similar evolution occurs in vaccinosyphilitic chancre. The vaccinal eruption appears and runs its regular course. Afterward, toward the twenty-fifth day, the chancre makes its appearance beneath the crusts of even the cicatrices of the pustules. At a more advanced stage, syphilis may coexist with tuberculosis.

The result is hybrid clinical types and events difficult of interpretation.

Secondary Infections. The author has several times seen patients convalescent from one eruptive fever contract another. The second infection generally runs its regular course. More interesting are those cases in which diphtheria makes its appearance in the course of another disease, especially of scarlatina or measles. It is then a question whether this secondary diphtheria is really due to an additional infection from without or whether, on the contrary, it is dependent upon exaltation of the Loeffler bacillus already present in the throat as an innocent resident. Without absolutely rejecting the latter interpretation, I believe the former is true in the majority of cases, if not in all. Out of a total of 4030 patients affected with scarlet fever or measles that have been treated in my wards, only one case of secondary diphtheria was observed. This was in a woman who had been in a ward close to one where diphtheria cases were treated. It is well to recall that diphtheritic manifestations which, until a few years ago, were of frequent occurrence in hospitals for children, have become altogether rare since prophylactic measures and isolation of different classes of patients has been rigorously practised. It is, therefore, not unfair to conclude that secondary diphtheria originates by contagion.

Development of tuberculous manifestations subsequent to an acute infection is not rare. In most cases the course is rapid. At times the process is one of caseous pneumonia. More often, however, tubercles invade the whole organism.

Typhoid fever is not rare in consumptives. It runs its course in a regular manner. Subsequently, however, tuberculosis assumes an acute course.

The influence of erysipelas is more complex. Its influence on pulmonary tuberculosis is never favorable, and is at times harmful. As to its action upon local tuberculosis, principally upon lupus, opinion is divided because, perhaps, the results are variable. Erysipelas developing in an old lesion favors its cicatrization. It may likewise cause improvement in neoplasms, epitheliomata, and, above all, sarcomata. It acts in the same way in lymphadenia.

It may, therefore, be concluded that while, in the majority of instances, an intercurrent acute infection aggravates a pre-existing chronic infection, it may, in some cases, favor the healing of some atonic lesions.

Combined Infections of the Skin. In the majority of diseases affecting the skin or the mucous membranes communicating with the exterior, mixed infection is unavoidable, and it is often difficult to determine the part due to the main agent and that ascribable to auxiliary agents.

The rôle of secondary infections is of considerable importance in cases of variola. The pustules contain a great number of pyogenic microbes from cutaneous sources. When the patient dies the staphylococcus, and particularly the streptococcus, and at times the pneumococcus, are found in the organs. The question is to ascertain the respective rôle of the specific agent and of the secondary microbes. Is it not to the latter that the fatal termination is due? And can it not be assumed that the gravity of confluent variola depends mostly upon the extent of suppuration, absorption of secreted products in the pustules, and general infection of the organism by pus cocci? It is evidently impossible to precisely answer this question. All that can be said is that the microbe of smallpox is a genuine pus coccus, but one of special nature, since it produces pus particularly rich in mononuclear leucocytes. This fact authorizes us to limit the rôle of superadded agents. Clinical observation already pointed to this conclusion, for according as the subject is or is not partially immune—according, for instance, as his organism has or has not been modified by previous vaccination—suppuration runs its course or is cut short. Notwithstanding the presence of pus cocci in the pustules, the eruption is aborted.

Combined Infections in the Throat. What has just been said concerning the skin may be repeated with regard to mucous membranes. In this connection, scarlatina is the most interesting infection. Under its influence the streptococcus of the mouth becomes exalted and plays an important part in the genesis of early or tardy angina, of local complications, such as purulent coryza, abscess of the tonsils, adenophlegmons of the neck, or of complications in distant parts, such as nephritis. The presence of the streptococcus in the various complications observable in the course of scarlatina is so constant that certain authorities consider this microbe not a superadded agent but the actual cause of the malady. This opinion is not yet supported by absolutely convincing evidence. The case of Heubner, everywhere cited, who developed erysipelas as a result of having received in his face salivary particles from a scarlatina patient, demonstrates the exaltation of the microbe, but by no means

its specific rôle. There exist a few observations of patients convalescent from scarlatina who were attacked by erysipelas. The development of the dermitis without any contamination is another proof of the rôle played by the streptococcus, for facts of this sort, of which I have collected nine examples, are much rarer after other infections. As there is no absolute demonstration that the streptococcus is the cause of scarlatina, we may conclude that this microbe becomes exalted under the influence of an angina, and thus becomes capable of giving rise to various complications.

Similar considerations may be presented with regard to all affections of the throat. In cases of diphtheria, for instance, a great number of microbes are found in the false membranes. It is quite evident that there can be no pure diphtheritic angina. In order to be convinced of this fact, it will suffice to make a direct examination of the false membranes or to sow them on agar-agar. Microbic associations will always be found. Angina appears to be pure only when the cultures are made in serum. This medium being more favorable to the bacillus of Loeffler than to other microbes, the specific agent is the first to develop. Is it right, however, to conclude that the other bacteria are indifferent because they vegetate slowly or not at all in this medium? The tetragenus, for instance, is frequently encountered in anginas, whether diphtheritic or otherwise. It is seldom noted, because it develops poorly in serum; other culture media are required. Therefore, the questions put in reference to tetanus and gaseous gangrene may be asked with regard to diphtheria: Is the bacillus of Loeffler capable of developing alone? Is it not rather necessary that it should be assisted by common bacteria, the common pus cocci of the throat which prepare the soil for it?

In 193 cases of sore throat, 31 of which were diphtheritic, 46 non-diphtheritic, 116 scarlatinal, we made bacteriological researches on serum, on agar-agar, and by direct examinations. The results varied considerably with the modes of examination and the culture media. The fact is that all microbes have not the same aptitude to develop in such and such a medium. The exclusive presence of the bacillus of Loeffler upon a serum tube simply indicates that this bacillus possessed a great aptitude to vegetate in this medium and that its rapid development checked and prevented the multiplication of the other bacteria. Let another culture medium be employed, and the results may be entirely different. The following table may give an idea of this fact:

Summary of Seventy-seven Comparative Observations of Serum and Agar Cultures from Anginas.

	Diphtheritic anginas, 31 obs.		*Non-diphtheritic anginas, 46 obs.*		*Total 77 obs.*	
	Serum.	*Agar.*	*Serum.*	*Agar.*	*Serum.*	*Agar.*
Bacillus of Loeffler	31	16	..	..	31	16
Streptococcus	3	16	25	28	28	44
Tetracoccus	5	17	12	32	17	49
Staphylococcus	1	2	6	5	7	7
Pneumococcus	..	1	6	2	6	3
Oidium	..	2	..	1	..	3
B. subtilis	..	..	1	1	1	1
Undetermined cocci	3	2	7	2	10	4
Undetermined bacilli	1	2	10	13	15	15
Filaments	..	1	3	2	3	3
Spirilla	..	..	1	1	1	1

From the mouth and nasal fossæ microbes may enter the sinuses of the face, the salivary glands, and the middle ear by way of the Eustachian tube. The mouth seems to be even constantly infected in certain diseases like measles. The microbes, however, remain in a harmless state and give rise to no disturbance.

Combined Infections in the Respiratory Apparatus. Among the microbes frequently encountered in the saliva of healthy individuals there is one which, with the streptococcus and staphylococcus, plays a very important part in the development of secondary infections—viz., the pneumococcus. This microbe often becomes virulent in the course of the most varied infections and, notably, in erysipelas. It may produce various inflammatory lesions in the mouth. It must arrest our attention, however, on account of the complications which it may cause in the organs of respiration. It is known that it is the most frequent agent of the various thoracic complications of infectious diseases. The streptococcus, its companion in the buccal cavity, comes next. Among the bacteria of most frequent occurrence, we may also mention the micrococcus tetragenus, staphylococcus, pneumobacillus, colon bacillus, etc.

It may well be asked how these germs are able to invade the respiratory apparatus. The majority of authors believe that they are driven from the buccal cavity toward the lower respiratory passages. In a highly interesting work, Dr. Beco[1] opposes this view. Taking ground upon the fact that pathogenic species are encountered in lungs free from all apparent morphological alteration, and that these

[1] Beco. Recherches sur la flore bacterienne du poumon de l'homme et des animaux. Arch. de méd. expér., 1899, p. 317.

are the microbes which most frequently give rise to bronchopulmonary infections, he concludes that the germs were already present in the lungs, and had only to develop.

The argument is not convincing, however. The pneumococcus has been encountered in the lungs, but the researches were made on cadavers. It is therefore a question whether the microbe had not penetrated during the agony or the ten or twelve hours which passed between the moment of death and that of cultivation. This remark is supported by the fact that in two out of four cases of sudden death the lungs were found sterile. If, on the other hand, account is taken of researches pursued on animals, the conclusion is reached that the presence of the pneumococcus in the lung is exceptional. We continue, therefore, to believe that bronchopulmonary infections occurring in the course of diseases are, as a rule, due to buccal germs. The latter may be carried down with particles of saliva, or be dislodged by the current of air passing over the dried mucous membrane. Although microbes cannot be carried away by the inspired air when they are surrounded by fluid, conditions are changed when, under the influence of the primary disease, the secretions are scanty and the mouth covered with soot.

Whatever may be the mechanism governing their development, the secondary infections of the lung are generally due to the pneumococcus. This is true in cases of eruptive fevers, in diphtheria, typhoid fever, and even in erysipelas. It might be believed that in the last-named disease the pulmonary complication depended upon the streptococcus, that it was a case of pulmonary erysipelas. Such was the old view. It is, however, established at present that the streptococcus has no tendency to leave the skin. The pulmonary lesion is the result of secondary infection, depending upon the pneumococcus.

Combined Infections in the Alimentary Canal. Microbic associations are likewise constant in the digestive organs. Experimental researches have demonstrated their importance in typhoid fever and cholera.

With reference to cholera, the researches of Metchnikoff have well shown the auxiliary rôle of ingested bacilli and at the same time explained the resistance of certain persons and the immunity of certain regions. Sanarelli admits an analogous etiology for yellow fever. The same pathogenesis may be claimed for amebic dysentery. Although we admit the amebæ to be the specific agents of

one form of this affection, we also believe that an adjuvant rôle is to be attributed to the bacteria that swarm in the intestinal cavity and participate in all the morbid processes developing therein.

In most infections digestive disturbances appear which bring about an increased virulence of microbes colonized in the gastrointestinal cavity. This explains the development of mucomembranous enteritis consecutive to typhoid fever. Cases of appendicitis have also been mentioned as the result of the most varied infections. In order to resist the action of exalted microbes, the lymphoid structures of the appendix become the seat of an inflammatory process which is comparable to that observed, under the same circumstances, in the tonsils, and at times results in more or less profound lesions.

The digestive disturbances may, in their turn, act on the organism. The toxins elaborated in the intestine diminish the resistance of certain tissues and notably of the sebaceous glands. Hence, the frequency of furuncles in cases of excessive intestinal putrefactions. Both the old method of prescribing purges and the modern medication by antiseptics act, I believe, in the same manner. They diminish fermentation, and thus suppress the cause of secondary infection.

As soon as the microbes of the mouth or of the intestine become exalted, they are capable of invading the neighboring parts. Suppression or at least alteration of the secretions favors the immigration of the microbes into the organs connected with the digestive tube. Ancient clinicians had long remarked that parotiditis occurred particularly in grave fevers when the mouth was dry and repeated cleansing did not remedy the absence of secretions. These glandular inflammations have become rare with the advance of individual hygiene.

Secondary Septicemias. In certain cases bacteria tend to invade the lymphatic or blood channels and then produce septicemic manifestations of a general character, or they become localized in some organ and give rise to various inflammatory or, oftener, suppurative lesions.

When common bacteria invade the organism, no matter what the mode of entrance may be, three eventualities are possible: (1) In some instances the secondary infection assumes the gravest aspect and is expressed by a septicemia which develops without determined localizations and may rapidly terminate in death. (2) In other cases septicemia becomes localized in some viscus the disturbances of which may be predominant in the morbid process. Finally, the germs

may at times be destroyed and eliminated as fast as they penetrate; they may be found in the different secretions, but give rise to no appreciable symptom.

There has recently been described a septicemic form of typhoid fever due to secondary action of the streptococcus. This strepto-typhoid infection (Vincent), studied by Loison, Simonin, Arnaud, Vincent, and Wassermann, is characterized by irregularity of the fever-tracing, very marked acceleration of the pulse, and tendency to hemorrhages.

In certain cases septicemia is expressed by cutaneous eruptions. Rubeoliform, scarlatiniform, and polymorphous erythemata have been encountered in typhoid fever. In two such cases, Etienne and Gillet discovered staphylococcus in the blood.

Secondary bacteriemia is at times so frequent that, without the revelations of bacteriology, it would have been difficult to determine its nature. Such is the case in gonorrhea. It was natural to attribute all the secondary manifestations to the gonococcus of Neisser and conclude that this specific microbe is capable of emigrating from the urethra and giving rise to symptoms in distant organs, notably to arthrites. There are recorded observations in which the joints contained no other microbes than the gonococcus. Such is not always the case, however. It is not necessarily the gonococcus that produces the so-called metastatic phenomena. In many instances gonorrhea does no more than prepare the way for the entrance of the microbes of suppuration, and what is found in the articulations is a common pus coccus.

Septicemia may present a special aspect when it occurs at the time of decline of or convalescence from an infection. In some cases it is transitory, as primary septicemias sometimes are. It is even possible that certain disturbances of convalescence, which are too often attributed to fatigue or some error of diet, are aborted septicemias, as traumatic fever and milk fever are abortive forms of primary septicemia.

Septicemias of convalescence are often attended by more lasting manifestations, general disturbances, and cutaneous or visceral symptoms. The case is then one of septicemia with erythema, purpura, and, in more serious instances, with albuminuria, gangrenous lesions of the skin, etc.

These septicemias may at times simulate a secondary complication, notably a meningitis. During the cholera epidemic of 1892 the

author observed two cases of this kind,[1] and Dr. Siredey has published some analogous reports.[2] The patients die with the appearance of meningeal phenomena, without necropsy revealing the slightest alteration in the nerve centres or in their envelopes. On the other hand, however, bacteriology explains the mechanism of the occurrences. In one of the cases above referred to, experimenting with the cerebrospinal fluid and the liver, the author obtained pure cultures of an unidentified bacillus. In order to indicate its pathogenic action and putrefactive power, he called it *bacillus septicus putidus*. This microbe shall be repeatedly referred to because, on account of the lesions it produces in animals and of the activity of the toxins it secretes, it presents a certain interest from the standpoint of general infectious pathology.

When secondary infections are somewhat prolonged they may simulate a relapse. Senger, dwelling on this point, asserts that, in typhoid fever, relapses are often nothing else than septicemias. The intestinal ulcerations enable the other germs to do mischief which is too readily ascribed to a recrudescence of the primary disease. This conception deserves to be submitted to rigorous analysis, for it is very ingenious and in harmony with the actual data of general pathology. The humoral modifications occurring at the time of recovery should prevent relapses. On the other hand, it is conceivable that these modified humors may be inactive in the presence of some new pathogenic agent.

Secondary Localizations of Septicemic Processes. When common bacteria invade the organism they do not always produce a general septicemia. In some instances they may become localized in a viscus and give rise to inflammatory or suppurative disturbances. This fact raises two interesting questions: In the first place, in the presence of an inflamed viscus, the question is, whether the lesion is due to the primary process or to a secondary one. In the second place, it is necessary to learn whether the organ has been invaded by propagation or by general infection. For instance, let us suppose a suppurative lesion in typhoid fever. Without a bacteriological analysis it is impossible to affirm that it is a secondary lesion. G. Roux has shown, for instance, that the abscesses in the spleen may be dependent upon the typhoid bacillus. Valentini found no other

[1] Roger. Recherches bactériologiques sur un cas de septicémie. Soc. de biologie, Oct. 29, 1892. Septicémie consécutive au choléra. Rev. de méd., Oct., 1893.

[2] Siredey. Discussion sur le choléra. Soc. méd. des hôp., Nov. 4, 1892.

than Eberth's bacillus in the fluid of a purulent pleurisy. Fraenkel made the same statement with regard to a case of peritonitis. It has recently been further established that osteomyelitis consecutive to typhoid fever is often due to Eberth's bacillus.

Let us now suppose ourselves confronted by an acute nephritis supervening in the course of an infection. The first question to ask is whether this nephritis is ascending or hematogenic, viz., whether the microbes have made their way from the bladder through the ureters or whether they have reached the kidney through the blood-vessels. Pathological anatomy, by discovering the existence of old lesions in the bladder, and especially by pointing out the topography of the renal alterations, often enables us to solve the first problem. The next task is to determine whether the lesion observed is due to the principal microbe or to a secondary agent. Is the most interesting of all infectious nephrites, namely, that of scarlatina, dependent upon the specific microbe or upon the superadded streptococcus which is constantly found in the urine in cases of scarlatinal albuminuria?

To sum up, secondary infections, almost always due to common bacteria, are frequently observed in all infectious diseases. These secondary infections may be expressed by septicemias, symptoms of which are confounded with those of the principal disease or which impart to the primary process a peculiar character. A secondary infection may be localized from the beginning or subsequently in one or several viscera. Hence, a series of new manifestations occur whose nature can be determined only by bacteriological researches.

It is hardly necessary to dwell upon the importance and gravity of secondary infections. Whether septicemic or pyemic, general or localized, they may impart to the disease a character of malignancy by creating hemorrhagic forms, by giving rise to endocardites, nephrites, degenerations of the liver, and by localizing themselves in arteries and veins. Moreover, they may render prognosis graver. If it is true, for instance, that scarlatinal nephritis is due to a secondary infection, it is easily conceived that this additional infection is often graver and accompanied by more disastrous consequences than the primary disease.

Microbic associations, therefore, play a capital rôle in the development of diseases. The more profoundly we study the pathogenesis of infections the more clearly we recognize that adjuvant causes are required for the development of a specific microbe. Among these

adjuvant causes, a principal one is represented by the auxiliary microbic agents which set the disease in motion, explain certain symptoms, and cause various complications. These facts do not suppress the idea of specificity. For among the microbes which simultaneously develop, there is one which impresses upon the disease its particular stamp, its clinical physiognomy. The others are useful or indispensable auxiliaries, but do no more than add some features to the morbid process.

CHAPTER VI.

DEFENSES AND REACTIONS OF THE ORGANISM.

Means of Defense of the Organism against Infections. Rôle of the Lymphatic Glands and Omentum. Rôle of the Organs, Liver, and Lungs. Variations in the Action of the Liver upon Microbes. Means of Defense against Microbic Poisons. Rôle of the Various Organs; Rôle of the Liver. Modes of Elimination of Microbic Poisons. Reaction of the Organism against Microbes and Toxins. Mode of Production and Signification of Local Lesions. Inflammation. Production of Inflammatory Exudates. Importance of Diapedesis and Phagocytosis. Evolution and Reparation of Inflammatory Lesions. Mode of Production and Chemical Constitution of Serous Exudates. The Fibrinous Exudates and False Membranes.

The Defenses of the Organism against Infections.

When a pathogenic microbe attacks at any point of the organism, two events are possible: First, the microbe may be highly virulent or the organism in a weakened state. Consequently, no struggle takes place, there being no resistance on the part of the organism. The result is a general infection. Secondly, the invaded organism reacts and endeavors to arrest the invader or to circumscribe the infection. A local reaction is then produced characterized by an afflux of serum and leucocytes. In some instances the first barrier thus created suffices to kill the microbe, and the local lesion thus saves the economy.

Unfortunately, the latter is not always the case. The microbes too often overcome the first line of defense and gain entrance into the circulation.

Protective Role of the Lymphatic Glands and Omentum. If the microbes pass into the lymphatic vessels they may be arrested in the lymphatic glands. The interesting researches of Bezancon and Labbé and of Manfredi conclusively demonstrate the important rôle of these glands as defensive organs. This fact had been already indicated by clinical observation. In the course of the most varied infections, acute, subacute, or chronic inflammations, the glands corresponding to the affected regions swell, and inflammation is at times so intense as to present the appearance of spreading in the form of periganglionic edema.

In spite of their simple appearance, adenopathies may manifest special characters corresponding to the nature of the primary focus. The glands become indurated in cases of syphilitic chancre; they suppurate and become ulcerated in the case of soft chancre; they are caseated in tuberculosis, etc. However, adenopathies, especially in their first stage, must be considered as defensive reactions. Manfredi has demonstrated that the microbes during their sojourn in the glands lose part of their virulence, that is, they become attenuated.

These considerations regarding the rôle of the lymphatic glands lead to the question whether other parts of the organism similar in structure can play the same defensive rôle. Anatomists have come to consider the serous membranes as adnexæ of the lymphatic system. Let us consider the peritoneum, for example.[1] Since the investigations of Ranvier the greater omentum is regarded as an extended lymphatic gland. Histological researches have shown that the cells contained in this portion of the serous membrane actively proliferate when a more or less virulent microbe is introduced into the abdominal cavity. When a moderately virulent culture, for instance, a culture of staphylococcus aureus, is injected beneath the skin, this culture gives rise to extensive suppuration; but when the same amount is introduced into the peritoneum, no symptoms are observed. This fact demonstrates, contrary to what was once believed, that a healthy serous membrane resists infection better than does the subcutaneous cellular tissue. It must be noted, however, that the animal which thus presents no disturbance shows some modifications in the greater omentum, because the inoculated microbes pass from the peritoneum to the greater omentum. When small foreign bodies are introduced into the peritoneum, most of them are gradually pushed by the intestinal movements toward the greater omentum and there become localized.

It may, therefore, be concluded that the greater omentum plays an important rôle in the protection of the peritoneum. Experiments have shown that its extirpation does not altogether abolish, but only weakens, the resistance of the peritoneum which, while sufficient to prevent infection of the organism by greatly attenuated microbes, is no longer strong enough to resist virulent microbes.

There are three defensive barriers opposed to the exalted microbes

[1] Roger. Rôle protecteur du grand épiploon. Soc. de biologie, Feb. 19, 1898.

of the digestive tract. While these agents tend to pass through the intestinal walls, they meet numerous lymphoid structures which hinder their progress. Should they overcome this first line of defense they may enter the chyliferous vessels, but they are then arrested by the mesenteric ganglia. If they enter the portal vein they meet the liver, which, as will presently be shown, is capable of arresting and destroying them. If they succeed in penetrating the intestinal walls, as is the case especially in young children, they are rapidly destroyed in the peritoneum, the protective rôle of which depends chiefly upon the greater omentum.

Protective Role of the Liver and Lungs.[1] When microbes penetrate by way of the stomach or intestine they pass into the portal vein and traverse successively the liver, the right heart, the lungs, and the left heart, to be thrown thence into the general circulation. In all other cases they first encounter the lungs.

Whatever their mode of penetration may be, microbes that have reached the blood rapidly disappear from the main bloodvessels. At the end of ten or fifteen minutes they are no longer found in this location, even though intravenous inoculation has been practised. The blood, then, represents an inhospitable medium for bacteria, which must abandon it and take refuge in the capillaries of the organs. Here the struggle between the organism and the pathogenic agents is carried on. The latter begin to multiply and secrete toxic substances which may insure them victory, while the cells of the body endeavor to exert their protective rôle, either by producing germicidal or antitoxic substances, or by taking up and digesting the microbes.

Two hypotheses are possible: Firstly, it may be assumed that the various phases of the struggle are alike in all the capillaries. Either the microbe or the organism will triumph, and the ultimate result will be the sum of the partial results of the same character. Or, secondly, it may be supposed that the phenomena vary from one capillary network to another; that the effects of the struggle are not identical in all the organs, but in some of them the microbe is victorious, in others the cell. If so, the events become more complex. The final result will be the sum of the partial results of different characters.

[1] Roger. Sur le rôle protecteur du foie coutre l'infection charbonneuse. Soc. de biologie, Oct. 9, 1897. Les organes protecteurs coutre les infections. Presse méd., June 15, 1898. Le rôle du foie dans les infections. Presse méd., Dec. 21, 1898. Le rôle protecteur du foie et du poumon. Cinquantenaire de la soc. de biol., Dec. 27, 1899.

These theoretical considerations lead to the question whether differences occur in the evolution of infectious diseases according to the vessel by which the culture is introduced. Experimenters generally inject the microbes through some peripheral vein. The pathogenic agent then first passes through the capillaries of the lung, to subsequently reach the general circulation. I have thought that the virulent injections should be practised through five different channels.

The author made inoculations by the distal end of the common carotid artery in order to determine the rôle of the cerebral capillaries; by the distal end of the femoral artery, in order to study the influence of a more common network; by a branch of the portal vein, to study the action of the liver; by a peripheral vein, to learn the rôle of the lungs, and, finally, by the central end of the aorta (central end of the carotid artery).

In making these injections care should be taken not to produce any local lesion at the point of injection and not to use cultures of too great virulence. The evolution of a local lesion would confuse the results, and the capillary networks would prove insufficient barriers against a culture of too great energy, so that the microbes would rapidly pass through them and produce a general infection, evolving in the same manner, irrespective of the mode of entrance.

The microbes employed by the author were the bacillus anthracis, the staphylococcus aureus, the streptococcus of erysipelas, the colon bacillus, and, finally, a more highly organized parasite, *oidium albicans*.

The animals which received the virus of anthrax by the aorta succumbed first. Those which were injected through some peripheral vein survived somewhat longer, which indicates a slight protective action of the lungs. This action, however, was not noticeable when more energetic cultures were employed. The injections practised through the carotid artery permit a somewhat longer survival than the intravenous inoculations. This result is interesting, as it leads to the belief that the nerve centres are capable of hindering anthrax infection.

It is to be recognized, however, that the differences observed according to the vessel by which the anthrax virus is injected have so far been of little consequence. While a few animals resist a little longer than others, all succumb. The twenty animals which the author inoculated through the aorta, peripheral veins, the femoral

or the carotid arteries, died at the end of a period varying from thirty-six to forty-eight hours.

The results are altogether different when the anthrax passes through the liver. Of twelve animals which received considerable amounts of anthrax culture by the portal vein, only three died. The liver, therefore, possesses the power to arrest the anthrax bacilli and destroy them. This organ plays an important part in the protection of the organism against anthrax infection. A dose of $\frac{1}{8}$ of a c.cm., injected by a peripheral vein, killed a rabbit of 2345 grams in thirty hours, while a dose of 8 c.mm., introduced by a portal vessel, was not sufficient to kill a smaller rabbit, weighing 1915 grams. This demonstrates that an amount of anthrax bacilli sixty-four times greater than that which kills through the peripheral veins is completely annihilated by the liver.

The protective action of the liver was as well evidenced in experiments with the staphylococcus aureus.

The sample employed, which was highly virulent, was diluted with bouillon and injected, as was the anthrax, by five different vessels. Contrary to the preceding results, the animals inoculated by the distal end of the carotid artery succumb first. The brain, therefore, represents an excellent culture medium for the staphylococcus. In the second place, the animals injected by the aorta or the femoral artery died. Those which received the virus by peripheral veins survived longer, and, finally, those which received it by the portal vein resisted the inoculation.

When we come to the streptococcus, we find that the liver exerts no protective action. This microbe finds in the parenchyma of the liver excellent conditions for vegetation, and the animals injected by the portal vein are generally the first to succumb. Those which have been inoculated by the aorta, the carotid, or the femoral artery die shortly after. As to the animals which have received the virus by the peripheral veins, they die tardily, or, if the virus is not too active, they may survive.

Of the author's twenty rabbits inoculated by the various vessels, all succumbed, while out of eight animals injected by the peripheral veins, three survived.

The lungs, therefore, represent a protective organ against the streptococcus. They play a rôle similar to that which the liver fulfils with regard to the *bacillus anthracis* or the *staphylococcus aureus*. There is this to be noted, however, that the destruction of

pathogenic agents by the lungs is less active. This organ does not neutralize more than one fatal dose.

With the colon bacillus, the results seem somewhat strange. The animals inoculated by the portal vein or the carotid artery are the first to succumb. Those which receive the virus by the aorta resist quite frequently. It must be admitted, therefore, that one of the organs tributary to the arterial system destroys the microbes. It is a curious fact that the liver, far from destroying this microbe, offers it an excellent medium of culture. This result explains well the frequency and gravity of hepatic infections of gastrointestinal origin.

In order to impart a more general character to his researches, the author undertook some experiments with cultures of *oidium albicans*. The animals injected by the carotid artery are usually the first to die. The lungs very slightly retard the course of the infection. The liver and the kidneys arrest great quantities of the parasites and prevent extension of the process. These organs very efficiently protect the economy.

The following table presents a résumé of the results of the author's researches on the protective rôle of the organs. It indicates the effects of virulent inoculations and their variations according to the vessels by which the cultures are injected:

		Bacillus anthracis.	*Staphylococcus.*	*Streptococcus.*	*Colon bacillus.*
Death	very rapid	Aorta Femoral artery	Carotid artery	Portal vein	Portal vein
	more or less rapid, but constant	Peripheral veins Carotid artery	Carotid artery Aorta Femoral artery	Portal vein Aorta Carotid artery Femoral artery	Carotid artery " " " " " "
	inconstant	" "	Periph'l veins	" "	Peripheral veins
Survival	frequent	" "	" "	Periph'l veins	Aorta
	almost constant	Portal vein	Portal vein	" "	"

		Colon bacillus of dysentery.	*Bacillus of dysenteriform enteritis.*		*Oidium albicans.*
			Old cultures	Fresh cultures	
Death	very rapid	Portal vein	Portal vein	Periph'l veins	Carotid artery
	more or less rapid but constant	Peripheral veins "	Portal vein Periph'l veins	" " Periph'l veins	Aorta. Aorta
	inconstant	"	" "	" "	Peripheral veins
Survival	frequent	"	" "	Portal vein	Portal vein
	almost constant	Portal vein	" "	" "	Renal artery

Modifications of the Action of the Liver upon Microbes. The protective action exercised by the liver toward infections seemed to

the author deserving of complementary researches. It was of interest to learn what occurred under various experimental conditions. He was led to study the influence of fasting, of microbic associations, and of certain substances, such as glucose, sodium bicarbonate, and ether. Excepting one series in which an anthrax culture was employed, staphylococcus aureus was always used.

Influence of Fasting. Under the influence of fasting the protective action of the liver diminishes, but quite slowly. After twenty-four hours of starvation it is exerted to a normal degree upon the anthrax bacillus. If the inoculations are made at the end of two or three days the antibacterial power is found to be weakened, but not completely suspended. Injection by the portal vein is still less rapidly fatal than that by some peripheral veins. This was demonstrated by the results obtained with the staphylococcus aureus.

Microbic Associations. We have already pointed out that the effects of microbic associations are due to the action of soluble substances. Thus it is that sterilized cultures of the *bacillus prodigiosus* favor, in a very marked degree, the pathogenic action of the staphylococcus. Their injection by a branch of the portal vein diminishes the protective action of the liver and, if the dose be sufficient, may even completely abolish it.

The fact that, under the influence of certain toxins, the protective rôle of the liver is abolished, may possibly explain, in part, the mechanism of microbic associations, which is as yet so little understood.

The Influence of Glucose. Solutions of glucose were used in two different ways. In some cases they were mixed with the culture and injected into a branch of the portal vein. In other instances they were administered by the stomach. In the latter case, its use was continued for two or three days in succession.

The results were complex. One important fact is that the influence of glucose differs markedly with the quantity introduced. When the sugar is directly injected into the blood by the portal vein, 3 to 5 grams suffice to diminish or suspend the hepatic action. When it is introduced by the stomach, larger quantities are required. Sixteen grams exert a decidedly harmful effect, but not as great as that produced by the portal injection of 3 grams. Smaller doses, on the contrary, exert a stimulating action upon the liver. Thus, in one of the experiments, an animal which had received 1 c.cm. of a very virulent culture through the vein, and which ingested

5 grams of glucose on each of two successive days, survived seven days, while the control died in eighteen hours.

The Influence of Bicarbonate of Soda. The author's experiments with sodium bicarbonate are not very numerous. The animals which received 5 grams by the portal vein or 10 grams per os rapidly succumbed to the injection of relatively small doses of staphylococcus by a mesenteric vein. It is probable that the amount of sodium bicarbonate injected was too great and, perhaps, by diminishing the dose, different results would be obtained.

The Influence of Ether. The action of ether likewise varies with the dosage. The author, therefore, multiplied the experiments. Thirty-four rabbits served for these series of researches. Some of these were used as controls; the others were treated in four different ways: Pure ether or a solution of the same was injected by the portal veins, or the animals were made to swallow one of these fluids. The solution of ether was prepared by agitating ether with a 20 per cent. solution of alcohol in water. The main fact resulting from these experiments is that five or six drops of pure ether introduced by an intestinal vein completely abolishes the action of the liver. It is probable that a part of the fluid diffuses and diminishes the general resistance, since in several cases the animals died more rapidly than those which had received the same dose by a peripheral vein.

When the method of ingestion is resorted to, it is found that doses of 1.5 c.cm. of ether diminish but slightly the action of the liver. In a dose of 1 c.cm. it seems to augment it. Smaller doses are best given diluted. When a dilution is directly injected into a vein it diminishes or abolishes the action of the liver in a dose of 1 or 1.6 c.cm. By ingestion, greater amounts can be administered: 2 to 3 c.cm. of the solution represent an excellent therapeutic dose for a rabbit of 2 kilograms. If the control dies rapidly, death of the animal treated with ether is delayed; if the control dies only after five or six days, the animal treated generally survives.

In brief, we conclude from these researches that the ingestion of small doses of ether increases the antimicrobic action of the liver.

All these experiments were made with the staphylococcus. The results obtained with the *B. anthracis* are analogous, although our experiments with the latter microbe are not numerous. It is well, however, to recall them, as they confirm the data already obtained with regard to the slight action of transitory fasting and the harmful influence of large doses of ether.

Defense of the Organism against Microbic Poisons.

Although the bacteria which vegetate upon the skin or in the respiratory passages are incapable of secreting noxious substances, this is not the case with those swarming in the digestive tube. It is often asserted upon the dictum of Cl. Bernard that the gastro-intestinal cavity is outside the organism. In fact, it is true that, in order to produce their effects, noxious substances must pass the barrier opposed to them by the intestinal epithelium. It must, however, be remembered that all conditions seem to combine to favor fermentations in the alimentary canal: fermentable materials, abundant fluids, and favorable temperature. Therefore, toxins analogous to those found in putrefactions are formed, as may be demonstrated by a study of the contents of the intestine or of the fecal matters. In infectious diseases, digestive fermentations are often intensified. There is an addition of poisons formed under the influence of pathogenic agents. Although the organism is constantly in danger of intoxication, the realization is in most cases prevented by the agency of various protective systems with which living beings are endowed.

Let us first consider the substances produced in the alimentary canal. Stich asserted that they are not absorbed. This greatly exaggerated view contains a certain amount of truth. The interesting researches of Queirolo, Denys, Abelous, Charrin, and Cassin establish the protective rôle of the intestinal epithelium. Its cells act equally upon vegetable alkaloids and certain microbic toxins, notably those produced by the colon bacillus. Poisons which escape this first barrier penetrate, in small amount, by the lymphatic vessels. They are then arrested and modified by the glands. The greater part, however, passes into the blood—*i. e.*, the portal vein—and is thus carried to the liver.

Action of the Liver upon Microbic Poisons. The action of the liver, so often studied and so well elucidated in cases of intoxications, seems far less clear with regard to microbic poisons. It is necessary, however, to distinguish the primary poisons from their derivatives. The action of the liver seems to be manifest upon the latter. The author recognized this fact as early as 1887, when studying the putrid poisons. The results of these experiments, reducing to kilogram of animal the quantities of extract of tissues injected, are summed up in the following table:

Fluid injected.	*Animal experimented.*	*Quantity introduced. Doses: Non-fatal.*	*Fatal.*
Dialized extract.	Healthy frog	300	..
	Frog without a liver.	..	300
Ethered extract.	Healthy frog	837	..
	Frog without a liver.	..	837
Alcoholic extract	Rabbit (peripheral vein).	..	91
	" (portal vein).	171	..
	" (portal vein).	..	216

It will suffice to remark that in the experiments upon the rabbit the relation of fatal doses, according as the injection is given by a peripheral vein or some branch of the portal vein, is as 2.36 to 1. It is, therefore, permissible to conclude that the liver arrests certain toxins extracted from putrid substances in the same manner as it arrests vegetable alkaloids. It can also act upon various bodies which often originate under the influence of microbes. Thus, according to Kochs, it shares with the kidneys the property of presiding over the modification of aromatic substances, and it is known that aromatic substances, notably phenol, thus lose much of their noxious power.

Microbes also give rise to the formation of ammonia, and the liver again comes to the assistance of the organism by arresting and neutralizing the ammonium salts, those at least in which the base is united with carbonic acid or some organic acid.

The study of putrid substances is particularly interesting because of the deductions that may be drawn for the history of intestinal fermentations. The substances originating in the digestive tube are, in fact, analogous to putrid substances, and the liver also acts upon these poisons.

The researches of Drs. Teissier and Guinard[1] have led to the unexpected conclusion that the liver exerts no protective action against the toxins of diphtheria and of pneumobacillus. Not infrequently, especially in the dog, the action of the poison is more energetic when it passes through the liver.

These results should not, however, be hastily generalized. The toxin of the dysenteric colon bacillus is neutralized by the liver. While 0.5 c.cm. injected into the peripheral veins of a rabbit kills this animal in two or three days, an amount four times greater introduced by the portal vein causes simply diarrhea. If greater quan-

[1] Teissier et Guinard. Recherches expérimentales sur les effets des toxines microbiennes et sur quelques influences capables de les modifier. Arch. de méd. expér., 1897, p. 994.

tities are administered, the liver is no longer capable of saving the animal, but prolongs its existence. Twenty cubic centimetres of a slightly weakened culture were injected into two rabbits. One, weighing 1825 grams, received the fluid by a peripheral vein, and died in collapse at the end of seven hours and a half; the other animal, weighing 1815 grams, received the poison by the portal vein, and died at the end of four days.

Action of the Various Organs upon Microbic Poisons. Recent researches establish that the lungs are able to attenuate the action of certain poisons. They act upon vegetable alkaloids and substances such as ammonium carbonate and fatty acids, which may be produced under the influence of certain microbes. However, its influence upon toxins, at least upon the diphtheritic toxin, seems to be *nil*. Animals comparatively inoculated by the carotid artery and the jugular vein die within the same period of time. The artificial circulation of the toxin through the lungs, even when prolonged for nearly an hour, in nowise modifies its action. No general conclusion should be drawn from this negative result, which must lead only to further investigations. It should be equally interesting to study the action which other parts of the organism—the spleen, the thyroid gland, the suprarenal capsules, the bone-marrow, the thymus, etc. —may exercise upon toxins. All that we know, since the remarkable experiment of Wassermann and Takaki, is that the brain possesses the power to fix and annihilate the toxin of tetanus.

Modes of Elimination of Toxins. As soon as microbic toxins enter the blood they probably undergo attenuation by oxidation or by neutralization exercised through certain principles which the leucocytes diffuse. As already stated, the kidneys also serve for the elimination of toxins. It may, however, be a question whether they simply excrete the circulating poisons or whether they previously submit them to some analysis. As a matter of fact, it has been demonstrated that infectious poisons contained in the organism are albuminoid substances. Those contained in the urine are of an alkaloid nature and, unlike the former, resist higher temperatures fairly well. It may, therefore, be asked whether the primary complex molecule is not broken up in the kidneys and does not leave in these organs its alkaloidal radical. This is no more than an hypothesis, but is worthy of verification. The remark might even be extended to autointoxications. In the course of uremia, the poisons contained in the blood and organs are likewise of an albuminoid

nature, while the urinary poison is not an albumin. It may, therefore, be supposed that the kidneys possess the power of breaking up the complex molecules of the products of disassimilation. In this manner, better perhaps than by an internal secretion, may be explained those cases of uremia which occur when the permeability of the kidneys is but slightly modified.

There are other modes of depuration. The respiratory apparatus eliminates volatile substances, probably the least important ones, some of them chemically defined. They impart to the breath the disagreeable odor observed in various infections, notably in those attended by increased intestinal putrefactions. The skin, likewise, may eliminate toxins, and, like the lungs, throws out volatile substances, among which sulphuretted hydrogen, ammonia, fatty acids, and acetone occupy the first rank. It may also eliminate a certain amount of noxious substances with the perspiration. We are not, however, well informed upon this point, and accurate experiments are lacking. It is well to remember that subcutaneous injections of pilocarpine often produce an improvement in the general state of patients suffering from diphtheria. It would be interesting to inquire into the properties of the increased perspiration secreted under these conditions. The eliminating rôle of the bile and gastrointestinal secretion is not any more clearly understood. The frequency of diarrhea and vomiting in animals which have received microbic toxins tends to demonstrate the existence of elimination through the alimentary canal. This hypothesis, to which occurrences in certain cases of poisonings also point, finds an additional support in the researches pursued by the author upon the toxins of the colon bacillus of dysentery. When the toxin was prepared with a sample of moderate virulence and was relatively weak, its introduction caused profuse diarrhea. When it was derived from a highly virulent sample, its action was more powerful, but there was very little, if any, intestinal flux.

Our knowledge concerning the passage of toxins into the milk is far from complete. A few observations, notably those reported by Sevestre, Lesage, and Siebert, tend to prove that the use of tainted foods may cause diarrhea in the mother and the nursling. In a case mentioned by Lesage the child, seven months old, died in forty-eight hours with symptoms of infantile cholera. Facts have been published demonstrating that even a benign intercurrent infection may impart to the milk a certain degree of toxicity and give rise to various

manifestations and particularly to diarrhea in the child. This has been observed in a case of phlegmonous tonsillitis (Henoch) and of vaccinia (Marfan). The experiments of Brieger and Ehrlich demonstrated that the toxins of diphtheria, tetanus, and typhoid fever pass into the milk. According to Pasquale and Michele, the same is true of those of tuberculosis. It must be remarked, however, that though the milk of sick women is at times contaminated, it may, in the majority of cases, be ingested without any inconvenience. In the writer's hospital wards he allows the mothers to nurse their infants when the infection from which they suffer is to be of short duration. A great number of women suffering from measles, scarlatina, mumps, erysipelas, sore throat, or even diphtheria, have continued to nurse without any harmful results for the nurslings. It has been necessary, in most cases, only to supplement the diminished secretion of the mother's milk by artificial feeding. As soon, however, as defervescence took place, the secretion was re-established. The author was inspired to this practice by the desire to avoid weaning the children definitely, since the effects of artificial feeding, especially among the poor classes, are only too well known.

The Reactions of the Organism against Infections.

Role and Signification of Local Lesions. Disease is the result of two contrary actions: In the first place, there is an attack of some pathogenic agent upon the organism. In the second place, a series of reactions calculated to hinder or neutralize the morbid effects occur.

To take a very simple example, let us suppose a pyogenic coccus to have been deposited beneath the skin. This microbe, finding in the interstitial fluids of the tissue conditions favorable for its development, rapidly multiplies. If it behaved like a simple inert body, it might form large colonies without producing any appreciable reaction on the part of the organism. Not so, however. The microbe elaborates soluble substances, some of which alter the surrounding tissues, and others, carried by the circulation, directly influence the entire organism. Reactions on the part of the organism are then aroused. If the substances elaborated by the microbe are very active they cause immediate death of the cells with which they come in contact. If less energetic, they give rise to an irritation which is expressed by responsive phenomena occurring in the cell and

without any intervention of the nervous system or the circulation. At the same time, the microbic substances and the products elaborated by the altered cells excite the surrounding vessels and especially the nerve terminations. By this mechanism a series of new morbid manifestations is produced, some of which, of a true reflex nature, return to the starting point of excitation, while others extend to the most distant parts of the organism.

Even when the lesion remains local and the toxins do not penetrate the economy the nervous system which, under normal conditions, assures functional synergy, suffices, under pathological conditions, to give rise to a series of morbid sympathies. However, toxins are almost always absorbed and, at points at which they reach the cells, they induce manifestations identical with those which occur at the point primarily invaded, viz., irritation of the cells, cellular reactions, excitation of bloodvessels and nerve terminations, reflex to the point of origin and reflex to distant parts. Finally, in a great number of instances, the figurate elements also penetrate the economy, settle at certain points, elaborate toxins, and the series of manifestations just described immediately recur.

If we consider the point primarily attacked by a microbe which has been deposited beneath the skin, for example, we see that at the point of its introduction a series of manifestations develop, resulting in the production of a local lesion. The latter represents a true barrier opposed to the invasion of the pathogenic agent. It is absent under two quite different circumstances. If the microbes meet an organism endowed with perfect immunity, the interstitial fluids exert a germicidal action upon them and prevent their development. A certain number of them are killed and the action of the others is inhibited to such a degree as to allow the leucocytes to completely eliminate them from the economy. In this instance the local lesion is not produced, because it would be of no use. The organism is so resistant that the invader is destroyed without any apparent struggle. Even in such cases, however, the destruction of bacteria is not as speedy as might appear at first sight. Certain non-pathogenic bacteria, especially if they are sporulated, may survive for a very long period of time. They remain as harmless foreign bodies, and behave altogether like insoluble substances. It is likely that they give rise to no defensive reaction because they are devoid of irritant secretions.

When the microbe is highly pathogenic or the organism non-

resistant the local lesion is likewise wanting, although for quite different reasons. The fluids then exercise no germicidal power, the microbe rapidly develops and, at the same time, secretes toxins, some of which, being absorbed, paralyze the nerve centres and prevent vasodilatation preparatory to serious exudation and diapedesis. Others exercise a negative chemotactic action, viz., repel the few phagocytes which approach the infected focus.

In cases in which the invading microbe is virulent the local lesion represents a salutary reaction. This reaction, however, like all other reactions, may become a new source of danger. A microbe which is implanted in a mucous membrane is capable of causing very serious accidents: for example, in the larynx, edema of the glottis; in the lungs, foci of fibrinous pneumonia and bronchopneumonia, which, by their extent, may prove fatal.

On the other hand, the effect may exceed the end. The organism at times mobilizes all its reserves upon slight alarm, and thus creates useless lesions. The congestion which surrounds a circumscribed pulmonary lesion must often be combated. The same is true with regard to diarrhea and effusions in serous membranes which sometimes reach considerable amounts in disproportion to the slight morbid cause that gives rise to all these effects. An interesting experiment of Gamaleia shows how excessive and dangerous organic reactions may sometimes become. This author produced in two rabbits a chemical irritation of the cornea. In one, reaction was allowed to follow its natural course, and terminated in an opacity. In the other case, the reaction was checked by various procedures which prevented the reflex congestion of the neighboring parts, and the cornea remained transparent.

The practical importance of these pathogenic data is readily conceived. Since therapeutics furnishes us with means capable of intensifying or attenuating reactionary phenomena, it is the duty of the clinician to determine the conditions under which the inflammatory reaction is produced, to recognize whether it is useful, insufficient, or excessive, and to respect, intensify, or moderate it accordingly.

Inflammatory Reactions. Whether or not a local lesion exists, microbes may invade the economy and settle in tissues and organs. In other cases they remain localized at the point of introduction, but secrete substances which diffuse and impregnate the economy. In both instances, visceral foci develop which, in their turn, become

the starting point of morbid reactions. These reactionary phenomena are known under the name of inflammation.

No term is oftener employed in medicine, and none, perhaps, has a meaning as much lacking in precision as the word inflammation.

Discarding the ancient theories, which are merely of historical interest, we find, at the present epoch, at least three different conceptions of the process in question: 1. That of Virchow, according to which inflammation is characterized essentially by cellular alterations, the vascular phenomena being of secondary importance. 2. That of Cohnheim, who sees in inflammation the sum of processes which begin by vascular dilatation and result in transudation and diapedesis (migration). 3. That of Metchnikoff, who defines inflammation as a salutary reaction tending to check infection by phagocytosis.

Whosoever, independently of theoretical discussions, looks for a characteristic of inflammation will see that this term must retain a very comprehensive meaning. As the question here concerns infectious diseases, we shall define inflammation as "*the ensemble of reactionary phenomena produced at the points irritated by microbic toxins.*"

These phenomena are multitudinous and may be classified as follows:

Alteration of fixed cells.

Reflex vascular disturbances.

Exudation and diapedesis.

Though not the first by order of occurrence, vascular disorders are first observed. They are easily appreciable, and the patient himself may notice them by the intensity of painful pulsations which he experiences. The clinician as well as the anatomist detects them without difficulty. It has, therefore, been asserted that congestion is the first stage of inflammation. As a matter of fact, it is preceded by a local change in nutrition. It is readily understood that, in reality, the presence of microbic poison modifies the medium which surrounds the cells, and, as life is an adaptation of the cells to the medium, when the latter changes the cells also must be modified. Their nutrition and, consequently, their activity cannot remain what they previously had been. There will first occur a dynamic change in the cell, which change will bring in its train further histochemical modifications. A lesion appreciable under the microscope may soon be detected, but it certainly is not the primary lesion. It is the result of a previous disturbance in cell function.

The excitation of nerve terminations by microbic toxins and by the products secreted by the already modified cells produces an active reflex vasodilatation at the point attacked. It is readily conceived that the more excitable the nervous system the earlier will congestion set in and, consequently, the more acute the process will be; that is to say, the greater will be the chances of a favorable evolution. A very simple experiment confirms this hypothesis. After the sensory nerves of a rabbit have been sectioned at the base of the ear, it is noticed that the subcutaneous inoculation of the streptococcus produces far graver lesions than in the intact ear.

According to the qualities of the pathogenic agent and the responsive aptitude of the organism, congestion may be effected in a slow and progressive manner or rapidly, almost suddenly. In the latter case, if an important organ is invaded, disturbances may suddenly become manifest. Everyone is acquainted with the violent pain and dyspnea attending acute congestion of the lungs.

Preceding and explaining serous exudations and diapedesis, acute congestion represents the first stage of inflammatory reaction. It is the beginning of a defensive act. Therefore, whenever reaction is tardy or weak we must stimulate the process. Three procedures, practised upon animals, enable us to obtain this result, and all three, by stimulating inflammatory reactions, favor healing of the lesions. First, section of the sympathetic, the influence of which upon the course of experimental erysipelas has been shown (Roger). Secondly, heat, by the agency of hot water circulating about the affected parts (Filhene). Therapeutics demonstrates the same favorable influence of hot applications in the treatment of erysipelas, and popular tradition has long taught us that a paronychia may be cured by plunging the finger in almost boiling water. In this case the temperature is not sufficiently raised to kill the microbe; the action is indirect through the congestion thus produced. Finally, as Dr. Carnot has pointed out, analogous results are obtained by submitting the inoculated animals to the influence of vasodilating substances, such as amyl nitrite.

Acute vasodilatation of the affected region is expressed by increased afflux of arterial blood and, consequently, acceleration of the circulation. The blood remains red in the veins. This result is important, as the leucocytes cannot leave the vessels except when the supply of oxygen is considerable. If the veins are compressed so as to slow the blood current, migration no longer takes place.

The exodus of leucocytes is preceded by an intermediate stage—second stage of inflammation—characterized by a slowing of the blood current. Then there occur what Cohnheim has described as "margination" of the leucocytes. These cells are seen to adhere to the walls of the veins, while in the capillaries they remain mixed with the red corpuscles.

Then begins the third stage, characterized by two events of prime importance, migration and exudation.

The leucocytes pass out of the smaller veins and capillaries. Those passing out through the latter route leave behind them small apertures through which a few red corpuscles may also escape. Not all leucocytes, however, are of the migratory variety. The lymphocytes are but slightly motile. The eosinophiles are endowed with sluggish motion. It is especially the varieties known as mononuclear and polynuclear neutrophiles that take the greatest part in the process and are particularly charged with the task of incorporating and digesting the microbes.

Coincidently with this migration there occurs a more or less abundant exudation consisting of a serous or serofibrinous fluid.

It is difficult to gain an insight into the mechanism of exudation. The mechanical explanation, at first accepted, is daily losing ground. It is admitted that venous stasis cannot account for the process and that ascites as well as hydrothorax and hydrocele must be attributed to a subacute or chronic inflammation of the peritoneum, pleura, or the tunica vaginalis, respectively. This view may be supported by the well-known experiments of Ranvier and those pursued by the author with Dr. Josué.[1] They have shown that ligature of the three efferent veins of the pinna of the ear is not followed by an effusion into the cellular tissue of the organ; but if at the same time the superior cervical ganglion of the sympathetic is excised, or if a few drops of a sterilized culture of bacillus proteus is injected, edema appears and persists for several days.

The inadequacy of the mechanical theory is further shown by the fact that the transuded fluid does not possess the same constitution as the blood plasma. The amount of salts is the same; but not so when the organic materials are considered, which seem to be furnished in a selective manner, as a true secretion.

When once out of the bloodvessels, the leucocytes proceed toward the points occupied by the microbes, and attack them. There has

[1] Roger et Josué. Note sur la pathogénie de l'œdeme. Soc. de biologie, July 27, 1895.

been much discussion in reference to the wonderful faculty with which they are said to be endowed or the kind of instinct they display. Recent researches demonstrate that the process is one embraced by a law of general biology. It is a phenomenon first studied by naturalists, and which Pfeiffer has described under the name chemotaxis, and of which Pekelharing and especially Bordet and Massard have shown the importance in animal pathology.

The soluble substances may be divided into three groups, according as they attract, repel, or exert no action whatever upon the leucocytes.

The majority of microbic products, and notably those of *staphylococcus aureus*, attract the migratory cells. The waste products of the cells of the economy do the same, a fact of the greatest consequence, since, from the very beginning and during the entire course of infection, microbes secrete substances which alter or kill the cells. On the contrary, the bacillus of chicken cholera exercises a negative chemotactic action, viz., it repels the leucocytes, at least those of the rabbit. Hence, the facility of microbic generalization.

The round cells which are found in an inflammatory exudate are not all derived from the blood. A certain number of them are furnished by the fixed cells of the connective tissue. In this connection the most interesting modifications are those of the giant elements described by Ranvier under the name *clasmatocytes*.

The fat of the adipose cells disappears and the elements resume a younger form. The endothelia likewise tumefy and return to their embryonal shape. In a word, the cells of mesodermic origin resume the functions which they exercised during the embryonal period. They recover their contractility and motility. This law seems to be applicable even to the muscular fibres. In this instance, however, more highly organized and, consequently, more sensitive elements are concerned. Therefore, the process of degeneration prevails over the reactionary phenomena.

In the midst of these profound modifications the epithelial cells do not remain intact. If the toxins are not very noxious the modification of the medium excites an increased activity on the part of the cellular element, and the phenomena of proliferation and notably karyokinetic figures occur. When, on the contrary, the toxins are highly energetic, the exchanges between the adulterated medium and the epithelial cells cause a series of functional disturbances which soon result in structural modifications. The cell may be killed at

the outest. It undergoes a particular fermentation which transforms it into a homogeneous mass resembling fibrin. This is known as coagulation necrosis. In case the element is still capable of reacting it presents the series of lesions which have been described as granular, pigmentary, hyaline, colloid or mucous, vitreous, caseous degeneration, and the like. It may be stated that, as a rule, degeneration occurs more frequently and earlier in epithelia than in connective tissue cells, for the reason that the structure of the former is more delicate and renders them more sensitive to various morbific influences.

The changes in the structure of cells revealed by the microscope result, as already stated, from functional disorder caused by modifications of the medium. It must be noted, however, that the nutritional disturbances in their turn influence the functions of the cells and notably their secretory activity. In cases of slight inflammation the cells react with energy, and their secretions are more abundant than under normal conditions. It will suffice to recall the intense salivation occurring in angina, the nasal flow in coryza, bronchial hypersecretion in inflammations of the respiratory passages, the diarrhea in enteritis, etc. When the process is violent, the reverse is observed. Secretions dry up: the tongue, the throat, the skin are dry, and urine is scanty

According to the nature or intensity of the process, the aspect of the inflammatory focus varies considerably. In its simplest expression the lesion consists of a serous exudate. In a higher degree, the fibrin coagulates, pseudomembranous deposits appear, and exudates are formed. If the toxins cause the death of a certain number of cells, the exudate undergoes a purulent transformation. In other instances bacteria produce therein fermentations similar to those characterizing putrefactions. The result is then a putrid effusion or a gangrene, according as the process occurs in the exudated fluid or in the tissue itself.

When the round cells are very abundant they are either scattered or form nodules. These embryonal masses may undergo a series of changes resulting in the production of simple or specific inflammatory granulations, such as infectious nodules, tubercles, syphilomata, lepromata, and the like.

As to reparation of the lesion, it may be complete or incomplete, viz., the tissue may resume its primary aspect or permanently retain lesions—indelible marks of the inflammatory process of which it has been the seat.

In the former case the lesions have been slight. A few cells perished in the struggle, but were picked up and digested by the macrophages. The survivors which, during the stationary period, were in karyokinesis, rapidly replaced the destroyed elements.

When, however, the process is intense or lasts for a long period of time, complete repair is impossible. The epithelial elements undergo too profound degeneration or perish in too great numbers. They are then replaced by connective tissue which, owing to its more elementary organization, is more resistant. A sclerotic tissue is thus produced which is at first traversed by numerous vessels, but the latter are not endowed with great vitality, and soon disappear, leaving the cicatrix in a state of dried tissue.

Serous Exudates. Serous exudations may be produced in the subcutaneous cellular tissue, in serous membranes, in parenchymas like the lungs, and less often in glands, as is the case in mumps. These exudates resemble the blood serum, but differ among themselves in their chemical composition. From this standpoint they have been divided into two classes: One comprises the inflammatory serosities, with a specific gravity reaching or exceeding 1018. These are remarkable for their richness in proteid substances and in fibrin, and coagulate spontaneously in the air. The second class comprises the mechanical dropsies, which contain but a small amount of nitrogenous substances, and do not coagulate unless certain elements, such as blood serum, ferment solution, or myosin are added.

Between these two extreme types there are numerous transitions. Belief in the importance of mechanical exudation is on the decline. It is asserted that even in cases of cardiac and Bright's disease serous exudations are often ascribable to the presence of bacteria. Undoubtedly all edemas should not be considered as inflammatory in nature. Venous stasis, cardiac incompetency, renal impermeability, and nervous derangements produce edemas independently of all inflammatory process. These facts are relatively rare, however, and most of the dropsies of serous membranes are held to be subacute inflammations. This view finds strong support in the fact that a great many microbes are capable of producing edema, as has experimentally been demonstrated with the *bacillus anthracis*, the bacillus of diphtheria, and the streptococcus of erysipelas. Nearly all the known microbes might be cited as capable of giving rise to subcutaneous edemas. Among the most important may be mentioned

the *bacterium lymphagogon* of Hamburger, the *proteus vulgaris*, whose soluble products have also an edemagenic influence, and the *staphylococcus aureus*. The last-named microbe is habitually considered as no more than a pus coccus. The author has noticed, however, that the subcutaneous inoculation of certain samples produces considerable edemas proving rapidly fatal, without the formation of pus. This result is not surprising, as most, if not all, of the microbes above referred to are apt to produce either edema or suppuration. In the former case the pathogenic agent is very virulent; serous exudation takes place, but the leucocytes cannot enter the field in sufficient numbers. In the latter case the microbe is less active, and migration is produced. In spite of appearances, the two processes are the same, differing only in degree. Anthrax, for instance, gives rise to a fatal edema in the guinea-pig and rabbit. In the adult rat, which is wellnigh refractory to the disease, an abscess is the result. Samples of staphylococcus when attenuated by successive cultures in artificial media become pyogenic. The same is true of the streptococcus. According to the degree of virulence of the sample or the resistance of the animal, the result is death without a local lesion, development of a fatal or curable edema, or production of a localized abscess of little gravity

Our knowledge concerning the chemical constitution of inflammatory subcutaneous edemas is very limited. All we know is that they differ from blood serum and lymph. They also differ from one case to another. They are not like the exudates of the serous membranes. It may, therefore, be concluded that they are due not to simple transudation, but to a sort of secretion, or at least, according to Jaccoud's expression, to a selective transudation.

Pleural exudates have more particularly attracted the attention of chemists, and the difference between inflammatory and simply dropsical effusions is clearly established. The latter process is to be understood as an inflammation of subacute or torpid character. Halliburton, who analyzed three cases of pleurisy and three of hydrothorax, gives the following demonstrative figures: specific gravity varied from 1020 to 1023 in the former instance; from 1012 to 1016 in the latter. Proteid substances, in pleurisy, oscillated between 34 and 52 per 1000. Fibrin amounted to 0.1 or 1; globulin, 12 to 30; and serin, 11 to 33 per 1000. In hydrothorax, proteid materials did not exceed 13 to 25; fibrin, 0.06 to 0.1; and serin, 7 to 18. Globulin varied from 4 to 7 per 1000. These results clearly

show that inflammatory exudates are denser, richer in protein, and especially in fibrin. It is but just to recall that Mehu's researches already pointed to these conclusions.

Pseudomembranes. It is customary in Germany to divide pseudomembranous processes into two groups, namely, superficial or croupous, and diphtheritic or profound. These expressions lead to confusion, and must be abandoned. They correspond, however, to a necessary distinction. As a matter of fact, in some cases the false membrane covers up a mucous membrane, of which it reaches the most superficial parts only. In other instances, the pseudomembranous exudate results from a necrosis of a more or less profound diphtheroid gangrene. The former process is realized by certain microbes, notably the bacillus of diphtheria. The latter process characterizes the destructive affections of toxic or microbic origin. Caustics, such as silver nitrate, and the most varied microbes may produce lesions of membranous character. Such is the case in ulcerating stomatitis, which actually represents a superficial gangrene of the mouth. Such is also the case in certain pseudomembranous cystites, pyelites, and enterites. The so-called false membranes are nothing more than parts or shreds of the altered mucous membrane.

There is, then, a marked difference between the two processes. The first is due to a general reaction of the organism; the second results from the necrosing action of a pathogenic agent. The former is characterized by the development of a concrete exudate upon the surface of a mucous membrane; the latter by exfoliation and expulsion of a pre-existing part which has been killed.

Leaving aside the description of diphtheroid gangrenes, which will be discussed elsewhere, let us now consider the true pseudomembranous process.

Under the habitual conditions of life this process may be considered as always dependent upon microbic infection. There is not, however, a specific diphtherogenic microbe. The false membrane represents a quite common reaction which may be excited by a number of bacteria. On the other hand, an agent capable of giving rise to the formation of a false membrane may in other instances produce an edematous exudation or a purulent focus. The difference depends upon the virulence of the microbe, the seat of the lesion, and the condition of the subject. These secondary influences intervene in all cases, even when Loeffler's bacillus is the agent concerned. The diphtherogenic action of this microbe is manifested only in parts in

contact with air, while subcutaneous inoculations produce only edema rich in fibrin, but no false membranes.

It is a well-established law that the figurate agents act only by their secretions. This law is applicable to the pseudomembranous processes. It has for a long time been believed that false membranes were not produced except under the influence of living bacteria acting upon an altered mucous membrane, and that the effect of the toxins was simply to induce a vasodilatation permitting the migration of leucocytes.

This conception has been abandoned in consequence of experiments pursued by Dr. Bayeux and the author and the confirmative researches of Dr. Morax. From these investigations it was shown that the diphtheritic toxin introduced into the trachea may be absorbed by the respiratory passage and give rise to a general intoxication. This is what occurs in animals highly sensitive to this poison, such as the guinea-pig. In rabbits, which are more resistant, a local reaction is often produced, resulting in the formation of a false membrane. It seems that, in this instance, the poison exhausts itself in local effects, since if the animal is sacrificed nothing but mechanical lesions, such as pulmonary emphysema, are found. Visceral lesions, which express general intoxication, are absent. We may, therefore, extend to toxins what is already demonstrated with reference to living microbes—viz., that the local lesion is the sign of attenuated poison. At all events, it is produced only when the animal is endowed with a certain degree of resistance.

Similar results may be obtained by operating upon other mucous membranes. It has been possible to produce pseudomembranous conjunctivitis, vulvitis, etc., by simply depositing the pure toxin of diphtheria upon the mucous membrane; but, as this has already been demonstrated with regard to suppuration, the more slowly the poison penetrates the greater is the success of the experiment.

Experimental results explain certain clinical facts in which false membranes were found to have extended far beyond the seat of microbic colonies. Such was the singular case which the author observed with Dr. Garnier.[1] A false membrane originated at the level of the superior vocal cords and epiglottis and extended uninterruptedly as far as the smallest bronchial ramifications. As may be seen in the figure below, the false membrane represents a perfect

[1] Roger et Garnier. Diphtérie tracheo-bronchique généralisée. Presse méd., Nov. 9, 1898.

mould of the bronchial tree. Below the ramifications of the third order the membrane was so thin that it was impossible to extract more than fragments. It is readily conceivable that tracheotomy failed to relieve the patient, since the obstruction of the respiratory passages was complete.

FIG. 1.



Diphtheritic false membrane.

The nature of the production was verified by cultures. At the time of admission of the sufferer a culture was made with exudates taken from the tonsils, and the presence of Loeffler's bacillus was demonstrated. At the necropsy fragments were taken from the middle intrapulmonary ramifications and cultivated. A small number of the bacilli were found. The culture tubes inoculated with the material from the last ramifications remained sterile.

The extension of the process cannot, therefore, be attributed to

the propagation of the bacilli, since their number diminished in proportion to the distance the points examined were from the larynx, and disappeared in the smallest branches of the bronchial tube.

To explain the production of pseudomembranes, several theories have been advanced. The simplest idea is to assume an exudation of a fibrinogenic substance which coagulates on contact with the air. Wagner asserts that false membranes are produced by the cells of the tissues which unite by means of prolongations. It is now generally admitted that an exudate is constituted, on the one hand, of fibrinogenic substance and, on the other, of altered cells. The fibrinogenic substance escapes from the vessels and finds the best conditions for coagulating—it is in contact with the air, it meets with dead leucocytes which here, as everywhere, play a great part in coagulation; it is spread out upon a mucous membrane the cells of which are diseased. From the time of Cohnheim and Weigert it has been known that epithelia as well as endothelia do not oppose the coagulating of exudations except when they are intact. At the same time a certain rôle is to be attributed to the cells of tissues which become fibrinified according to the process described by Weigert under the name coagulation necrosis.

Thus, made up at the expense of the fibrin of the blood and of the cells, false membranes appear under variable aspects. They may be found in serous exudates where they float in the fluid. In other cases they are more abundant and line the two surfaces of the serous membrane, and may cause them to adhere. Lastly, they are not infrequently seated upon the surface of a mucous membrane, adhering to it more or less intimately.

Should one of these pseudomembranes be stripped off, an ulcerated, slightly bleeding surface is exposed, which clearly proves that we are dealing not with a simple deposit, but a more profound lesion.

The detached false membrane is sufficiently resistant. It does not disintegrate when agitated in water, thus being distinguished from pultaceous layers or mucous accretions. It is dissolved by lime-water and by sodium hypochlorite; its richness in fibrin explains why it decomposes oxygenated water.

Under the microscope a false membrane is found to be composed of anastomosed fibrinous threads, sending out prolongations which attach themselves to the subendothelial tissues by a series of arcades. This explains why the production is adherent. The fibrin appears in the form of lamellæ, compact masses, or spiral threads. In the

midst of the fibrin can be seen mucin, fat, altered cells, and in most cases, numerous microbes.

The false membrane may grow by the addition of new layers of fibrin and be reproduced when it is stripped off. The considerable amount of fibrin which may thus be eliminated is not to be wondered at. Dr. Dastre has demonstrated how rapidly this substance is produced in the organism. If the greater part of the blood of a dog be defibrinated and again introduced into the vessels, it will soon be found that the blood has become as rich in fibrin as normal.

When a false membrane occupies the surface of a mucous membrane, that of the throat for instance, a time will come in fortunate cases when the secretions of the subjacent glands will detach the pseudomembrane and cause its exfoliation. The remaining adherent particles will be removed by the phagocytes. This process may be assisted by means of pilocarpine which, by stimulating glandular secretion, hastens exfoliation of the pathological membranes. In some instances the latter disappear in consequence of a histochemical transformation. They undergo a granular or hyaline degeneration.

In other cases in tissues, and particularly in serous membranes, the false membrane, instead of disappearing, becomes organized. The fixed and the wandering cells proliferate, and the tissue becomes vascularized. In this manner are formed adhesions which may subsequently be absorbed, or undergo sclerotic transformation, or become infiltrated with calcareous salts.

The production of false membrane must be considered as a phenomenon of defensive reaction. It is a barrier opposed to the penetration of microbes and toxins. In some cases it is a reinforcement of tissues, preventing their destruction under the influence of pathological causes. This is equally true as regards the false membranes developing upon serous membranes.

In this mode of defensive reaction, as in other instances, excess is often possible. The diphtheritic false membrane may, by reason of its location, cause grave and fatal disturbances of a mechanical order. The adhesions of serous membranes embarrass the movements of subjacent viscera, give rise to deformities, compress important organs or excretory passages, and thus bring in their train a whole series of morbid manifestations.

Although the process is somewhat different, the production of exudates rich in fibrin, as well as those produced by the pneumococcus, may be compared to false membranes. The expression

"croupous pneumonia," at times applied to the pneumococcic inflammation, suggests this analogy. We find the same pathogenesis for the pneumococcic exudates as for diphtheritic productions. The investigations of Carnot establish that they depend upon microbic toxins. Their signification is identical in both cases. They are lesions intended to protect the organism against the penetration of microbes and of toxins. On taking into account the nature of these two sorts of exudates, we reach the conclusion, which is equally that of Gilbert and Fournier, that fibrin plays a defensive rôle of considerable importance.

CHAPTER VII.

SUPPURATION.

Division of Pyogenic Microbes into Five Groups: The Habitual, the Specific, the Accidental, the Vegetable, and the Protozoic Pyogenics. Relative Frequency of Various Pyogenic Agents. Distribution of Pyogenic Microbes in and Outside the Organism. Causes Favoring Suppuration: Importance of Number and Virulence of Microbes; of the Mode of Entrance; of Previous Lesions. Generalization of Suppurating Processes. Amicrobic Suppurations. Rôle of Soluble Substances in the Production of Pus. Physical and Chemical Characters of Pus. Mode of Development and Evolution of Suppurations. Hot and Cold Abscesses. Suppuration in the Various Parts of the Organism.

From a histological standpoint, suppuration is essentially characterized by the formation of an exudate containing very large numbers of round cells, more or less similar to leucocytes. These cells, therefore, became the first subject of research. Virchow believed they were derived from the fixed cells of the inflamed tissue. Cohnheim contended that pus corpuscles were nothing else than leucocytes which had left the vessels by migration. Each of these conceptions, as we shall see later, contained some part of the truth, but they did not solve the problem. It was necessary to discover the influences which caused the round cells to accumulate in an organ or tissue and the conditions under which inflammation terminated in suppuration.

During the epoch of Virchow it was admitted that any cause of irritation could induce suppurative inflammation. Later, it was asserted, on the contrary, that the various physical, mechanical, and chemical excitants are incapable of producing pus unless the foreign body introduced has special specific properties, viz., unless it serves as the vehicle of pyogenic microbes. Caspard, as early as 1822, and after him, Gunther, d'Arcet, Castelneau, and, above all, Sedillot, showed by experiments that, when injected beneath the skin or into the serous membranes, pus can produce suppuration, but did not demonstrate the specific nature of the process.

In 1872 Chauveau pointed out that the phlogogenic power of pus depends not upon the serum, but upon the solid parts; that the pus corpuscles possess a special property, while the mineral substances and the cells derived from the lymphatic glands are not capable of

giving rise to suppuration. It was thus established that all foreign bodies are not pyogenic. The nature and causation of the primary focus remained to be determined.

Lister admitted the rôle of germs without, however, believing that their intervention is indispensable. He supposed that suppuration may be referable to other causes, for instance, the action of chemical agents or the influence of some nervous disturbance. From that epoch onward attention was called to the rôle of microbic agents. In 1872, Klebs described a *microsporon septicum* capable of producing pus. In 1875 Bergeron noticed the presence of *vibrions* in the pus of acute abscesses. Kocher, studying a great number of abscesses, constantly found bacteria, and was thus led to the conclusion that there is probably no suppuration without microbes. This was also the opinion of Cheyne, Koch, and Cornil, and it generally seems to be true in practise.

Under certain conditions almost all microbes are capable of exerting pyogenic action. In order to facilitate description, however, we may artificially divide them into four groups: First, the habitual agents of suppuration, the pyogenics, properly so-called. Not that they are found only in purulent foci—since the staphylococcus has been met with in serous exudates, in pleurisies, in rheumatism, and the same is true of the streptococcus—but because we consider that their most characteristic property is the production of pus in the organism. Secondly, unlike the common pyogenic microbes which are abundantly distributed in nature, and often live as epiphytes or saprophytes, there are specific pyogenics, always pathogenic and always creating suppurative lesions. This group includes five species: the diplococcus of cerebrospinal meningitis, the micrococcus of gonorrhea, the bacillus of soft chancre, the bacillus of glanders, and the bacillus of bubonic plague. The third group comprises microbes which are quite different from the preceding—specific agents which habitually produce well-defined diseases, such, for instance, as the microbes of typhoid fever or of influenza. These become pyogenic only under special conditions, to be referred to later. Finally, in a fourth division it is convenient to group those pyogenic agents which do not belong to the class of bacteria.

The following table, although incomplete, comprises the principal parasites capable of inducing suppuration:

1. Pyogenic Bacteria.

Staphylococci.

Staphylococcus pyogenes aureus (Rosenbach).
Staphylococcus pyogenes citreus (Passet).
Staphylococcus pyogenes albus (Rosenbach).
var.: Staphylococcus salivarius pyogenes (Biondi).
Staphylococcus of Almquist.
Staphylococcus pyosepticus (Hericourt and Richet).
Staphylococcus epidermidis albus (Welch).
Microbe of the Biskra button (Duclaux).

Streptococci.

Streptococcus pyogenes (Rosenbach).
Streptococcus erysipelatis (Fehleisen).
Streptococcus articulorum (Loeffler).
Streptococcus pyogenes malignus (Flügge).
Streptococcus septicus (Nicolaier and Guarnieri).
Streptococcus septopyemicus (Eberth and Wolff).
Streptococcus conglomeratus (Kurth).
Streptococcus ramosus (Roger and Weil).
Streptococcus of acute Bright's disease (Manneberg).
Streptococcus equi (Schutz).
Streptococcus ruber (Lundstrom).
Streptococcus of contagious mammitis of the cow (Nocard and Mollereau).
Streptococcus septicus liquefaciens (Babes).
Streptococcus pneumoniæ (pneumonococcus of Talamon-Fraenkel).
Micrococcus pyogenes tenuis (Rosenbach).
Micrococcus pneumoniæ (Ortner).
Microbe of pneumonia of the horse (Schutz).

Other micrococci.

Micrococcus tetragenus (Koch, Gaffky).
Micrococcus gingivæ pyogenes (Miller).
Micrococcus endocarditis rugatus (Weichselbaum).
Micrococcus subflavus (Flügge).
Micrococcus pyogenes fetidus (Veillon).
Staphylococcus parvulus (Veillon and Zuber).
Diplococcus reniformis (Cottet).
Micrococcus of gangrenous mammitis of the lamb (Nocard).
Micrococcus of necrosis of the mouse (Koch).
Micrococcus of pyemia of rabbits (Koch).
Micrococcus of progressive suppuration of rabbits (Koch).

Bacilli.

Bacillus coli (Escherich).
B. lactis aerogenes (Escherich).
B. pyogenes fetidus (Passet).
B. burci.
B. endocarditis griseus (Weichselbaum).
B. enteritidis (Gaertner).
Pyobacillus Fischeri.
Pneumobacillus (Friedlaender).
B. meningitidis purulentæ (Neumann and Schaeffer).
B. sycosis (Tommasoli).
Bacillus of noma (Schimmelbusch).
B. pyogenes soli (Bolton).
B. dentatis viridans (Miller).
Proteus Zenkeri.
Bacillus fetidus liquefaciens (Lenz).
B. nephritidis (Letzerich).
B. pulpæ pyogenes (Miller).
B. gingivæ pyogenes (Miller).
B. capsulatus (Chiari).
Proteus vulgaris (Hauser).
Proteus mirabilis (Hauser).
Proteus pleomorphus (Karlinski).
Bacillus saprogenes II. (Rosenbach).
Bacillus saprogenes III. (Rosenbach).
B. pyogenes gazeigenes (Levy, Fraenkel).
B. perfringens (Veillon and Zuber).
B. ramosus (Veillon and Zuber).
B. serpens (Veillon and Zuber).
Bacillus fragilis (Veillon and Zuber).

B. fusiformis (Veillon and Zuber).
B. furcosus (Veillon and Zuber).
Streptobacillus pyogenes floccosus (P. Courmont and Cade).

2. Specific Pyogenic Bacteria.

Diplococcus intracellularis meningitidis.
Gonococcus.
Bacillus of soft chancre.
Bacillus of glanders.
Bacillus of the bubonic plague.

3. Accidental Pyogenic Bacteria.

B. anthracis.
B. of gaseous gangrene.
B. of symptomatic anthrax.
B. of hemorrhagic septicæmia.
B. of purulent rhinitis of the rabbit.
B. of tuberculosis.
B. of pseudotuberculosis.
B. of influenza.
B. of typhoid fever.

4. Pyogenic Plants.

Streptothrix or oöspora asteroides.
Streptothrix or oöspora Hofmani.
Streptothrix or oöspora Gruberi.
Actinomyces (oöspora bovis).
Oöspora maduræ.
Aspergillus fumigatus.
Penicillium.
Mucor (corymbifer ?).
Botrytis (?)
Various yeasts:
Cryptococcus farcinosus.
Oidium albicans.
Trichophyton mentagrophytes.
Trichophyton felineum.

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5. Pyogenic Protozoa.

Ameba coli.
Protozoon of variola.
Protozoon of varicella.
Protozoon of vaccinia.

1. Pyogenic Bacteria.

Staphylococcus. The type of the habitually pyogenic microbe is represented by the *staphylococcus pyogenes aureus*. It was discovered by Ogston in 1881, and fully described, in 1884, by Rosebach. It is a facultative anaërobe developing readily in the majority of media employed in bacteriology. Examined under the microscope, the staphylococcus aureus, as well as albus and citreus, appears in the form of small, rounded elements, measuring from 0.7μ to 1.5μ. The smallest elements are seen in old cultures, the largest in cultures kept at 109.4 F. (43 C.). In pus the cocci are disseminated in the form of monococci or diplococci. In cultures they are generally united in masses, presenting at times the aspect of a bunch of grapes. Hence, the name given to this species. More frequently, however, these cocci are grouped in such a manner as to form large anastomosed bands circumscribing empty spaces.

The chromogenic function which characterizes the staphylococcus aureus has no specific value. This microbe ceases to secrete its pigment when cultivated in the absence of air, or when small amounts of antiseptic substances, such as antipyrin, are added to the medium, or when the culture is exposed to strong sunlight. The different staphylococci are, therefore, considered rather varieties of one species. Owing to its greater power of multiplication and more energetic pathogenic potency, the staphylococcus aureus is the leading species. Next comes the staphylococcus citreus, followed by the albus, whose cultures are not pigmented. Starting with the aureus, it is easy to obtain the colorless variety. The reverse is less frequently realized. Dr. Netter has, however, seen a *staphylococcus albus* converted into aureus.

Streptococcus. A great number of streptococci have been described. The present tendency, at least in France, is to regard them as varieties of a single species. In fact, the different characters described by authorities are rather uncertain and may disappear in successive cultures. Researches in serotherapy, however, lead us again to subdivide the group, since the serum of an animal immunized against one variety does not combat infection by all streptococci. The presence of micrococci in the form of chains had been noticed by Coze and Feltz in various organic fluids. Pasteur and Doleris subsequently discovered similar elements in puerperal infection. Their presence in pus was pointed out by Ogston, then by Rosenbach and Posset, who made a complete study and endeavored to differentiate it from the streptococcus of erysipelas, discovered by Fehleisen. The streptococcus develops quite readily in various media employed for cultures. In agar-agar it generally vegetates in the form of very small, rounded, somewhat hemispheroid, semitransparent, or opaque white colonies. These colonies are generally isolated, except in very active cultures in which they may become confluent.

The streptococcus is a facultative anaërobe. Some specimens develop more luxuriantly without than with air and, withal, better preserve their virulence and secrete more active toxins. Under the microscope the streptococcus appears in the form of chains made up of four to forty elements. The chains, which are rather short in solid media, are much longer in liquid media, and particularly in serum. Authorities have described different species of this coccus according to cultural characters, morphology, and pathogenic action.

Behring first divides streptococci into two groups according as the

chains are long or short. The short one, *streptococcus brevis*, is a saprophyte; the long, *streptococcus longus*, is divided as follows:

1. S. rendering bouillon turbid.
   S. of erysipelas.
   S. pyogenes.
   S. of anginas.
2. S. not rendering bouillon turbid.
   a. Producing a mucous deposit.
      S. of phlegmon.
      S. of bronchopneumonia.
      S. of puerperal infection.
   b. Producing flocculi.
      S. of scarlet fever (*S. conglomeratus*).
      S. of grave pyemia.
   c. Producing large masses adherent to the walls of the tube.
      S. of equine pneumonia.

It would be more rational to base a classification upon results obtained by inoculations into animals than upon modifications observed in the form of the elements and appearance of the cultures. Under these conditions four varieties of streptococci should be admitted: saprophytic, septicemic, pyogenic, and erysipelatogenic. Experimental and clinical studies demonstrate, however, that the pathogenic varieties easily fall into the rank of saprophytes. Reciprocally, most of the non-virulent cultures are capable of exaltation. The microbe first becomes capable of producing pus, then of giving rise to erysipelas, and, finally, to septicemia. This result having been verified by many authorities, has led to the admission of two principal species, pyogenic and erysipelatogenic, in which all the other varieties have been included.

Pneumococcus. The belief that the pneumococcus is related to the streptococcus has gradually gained ground. Some bacteriologists even consider it to be a variety of true streptococci. In support of this view, it may be recalled that there are certain microbic forms constituting transitions between the extreme types. Until the contrary is proven, however, it is more rational to consider the pneumococcus of Talamon-Fraenkel as a different species. Its pyogenic rôle needs no further demonstration. There is already abundant observation showing that this microbe is capable of producing suppuration in the lungs or elsewhere. Contrary to an opinion formerly advanced, it is now known that postpneumonic abscesses may be created under its influence without the co-operation of any other microbe.

There are other pyogenic micrococci, among which the *micrococcus*

tetragenus occupies an important place. Chauffard and Ramond believe that it can produce septicemias, and I have frequently found it in cases of sore throat, in which, however, it was associated with various other microbes (p. 44). Being almost constantly present in the buccopharyngeal cavities, the tetragenus is found in the abscesses developing in this region. It is met with particularly in dental abscesses, cervical adenites, otites, mastoidites, suppurations of nasal origin, pulmonary abscesses, purulent bronchitis, and in the pus of tuberculous cavities. Karlinski has found it in tubercles, and Babes in pyohemia. I have found it in the thick, yellow discharge of an otitis developed in a child convalescent from scarlatina.

The other pyogenic micrococci are far less important.

Pyogenic Bacilli. The *bacillus coli* unquestionably heads the list of pyogenic bacilli. Abundantly distributed throughout the alimentary canal, it is naturally met with in suppurations occurring in and around the digestive tract and around the genito-urinary apparatus. It may, however, easily migrate from these primary foci and induce secondary suppurations in distant parts, or even a general infection —a pyemia.

The morphology of this bacillus is very variable. It most frequently occurs in the form of small rods, with rounded ends, measuring from 2μ to 4μ in length and 0.7μ to 1μ in breadth. It sometimes appears in the form of oval elements, which at first may be mistaken for micrococci. At times it is isolated, at others grouped in pairs, or it becomes elongated to such an extent as to form filaments which are often constricted at several points in its length. Finally, if we add that there are motile and non-motile forms; that the appearance of cultures in agar-gar and gelatin and upon potato is not uniform; that the so-called specific characters are inconstant and variable; that some samples ferment sugar and others do not, and that certain cultures produce indol, others furnish none, it will be understood how delicate interpretation becomes. With the typical colon bacillus Gilbert has grouped and described the paracolon bacilli which present pronounced deviations from the classical type. It is certain that the group of colon bacilli includes species which will some day be differentiated. The reason division is not more advanced is that none of the properties seem to be absolutely constant. It is convenient, therefore, to include the various forms under the same denomination, as is done with the streptococci.

Among the bacilli at present believed to be related to B. coli there

is the *B. lactis aerogenes*, discovered by Escherich in the stools of infants. Close to this bacillus stands the pneumobacillus of Friedlaender. Between these two organisms pronounced analogies may readily be observed. The presence of a capsule is a character too contingent to be of specific value. The two microbes cannot be any better differentiated by their action upon animals, since we have shown that, contrary to classical opinion, the bacillus of Friedlaender is pathogenic for the rabbit. Hence, the attempt of eminent scientists, such as Denys, to regard the two bacilli as identical. The question is and will long remain a delicate one. Therefore, without pretending to offer a definite solution, I have thought it sufficient to point out the analogies of the two microbes and to recall the pyogenic power of the pneumobacillus. Akin to this microbe is the one described by Passet under the name *pneumobacillus ähnlicher*, which was found by the author in an abscess and which produces suppuration in animals, and, finally, the encapsulated bacillus which Chiari detected in suppurative nephritis, prostatites, otites, and meningites.

Anaerobic Pyogenic Bacteria. While common suppurations are generally due to aërobic microbes, the anaërobic seem to play a considerable rôle in the development of gangrenous or putrid abscesses and phlegmons. Levy isolated from a gaseous abscess a small anaërobic abscess which he failed to cultivate beyond the first generation. This is probably the same microbe which Fraenkel again met with in three cases. Inoculation of cultures gave rise to gaseous gangrene in animals—a new illustration of the relationship existing between suppuration and gangrene.

Examining sixty samples of pus, Lubinski found anaërobic bacilli twice. Similar findings have been made by various authorities who are at present inclined to admit that anaërobics play the principal part in the development of suppurations in the urinary apparatus (Albarran, Cottet), genital apparatus, at least in women (Veillon, Zuber, Dujon, Halle), and certain portions of the alimentary canal (Veillon and Zuber).

One of the most important bacilli isolated by experimenters seems to be the *B. ramosus*, which is supposed to be the chief agent in appendicitis. In conjunction with it we must mention the *B. perfringens*, analogous to or identical with the anaërobic bacillus of Levy and Fraenkel; the *B. fusiformis*, the *B. serpens*, the *B. fragilis*, the *B. furcosus*, and the *staphylococcus parvulus*. A detailed description

of all these species will be found in the interesting memoire of Veillon and Zuber.[1] It will suffice to note here that these various agents, when inoculated into animals, give rise to abscesses or phlegmons. Some of them, only slightly noxious when alone, become highly virulent when associated with other species. Such is the case with *B. serpens* when it is inoculated along with the *B. ramosus*.

Among the anaërobics which intervene in suppurations of the urinary passages the most interesting is the *diplococcus reniformis* (Cottet), which produces urinary and periurinary abscesses, pyonephroses, and cystites. By its morphological characters it resembles the gonococcus, with which it has probably often been confounded.

2. Specific Pyogenic Bacteria.

Five microbes at present make up this group. They differ from the agents which we have thus far studied in that they always give rise to suppuration and that this suppurative process has special characters previously established by clinical observation. Bacteriology has done no more than confirm the data of clinical experience.

The microbes of cerebrospinal meningitis, gonorrhea, soft chancre, glanders, and bubonic plague, although pyogenics, deserve to be grouped in a special class. The gonococcus resembles common pyogenics in some respects. Like the latter, it is said to be capable of vegetating as an epiphyte upon healthy mucous membranes. From this point of view, the bacillus of soft chancre or bacillus of Ducrey occupies a higher rank. Finally, the bacillus of glanders assumes a position of transition between the pyogenics and the specific agents, such as the tubercle bacillus.

3. Bacteria Accidentally Pyogenic.

Highly differentiated microbes, capable of producing well-defined diseases, give rise to no more than abscesses when they are attenuated or inoculated into animals not very sensitive by nature or rendered artificially more or less immune. Such, for instance, is the case with anthrax, the inoculation of which into old rats causes only an abscess. The same is true with regard to the virus of gaseous gangrene or symptomatic anthrax when inoculated into animals which have been subjected to incomplete vaccinations. An analogous example is furnished by the microbe of chicken cholera, which

[1] Veillon and Zuber. Recherches sur quelques microbes strictement anaérobies. Arch. de méd. expér., 1898, p. 517.

causes a speedily fatal septicemia in chickens and rabbits, but produces only a more or less extensive suppuration in guinea-pigs, while in man it gives rise to no more than a circumscribed abscess, as the author was able to observe in consequence of an accidental inoculation.

We need hardly recall that the bacillus of tuberculosis may become pyogenic. Everyone is acquainted with the frequency of cold, cutaneous, osseous, or articular suppurations in which no other parasite is found. What is accomplished by Koch's bacillus is equally realized by the bacillus of pseudotuberculosis. Either tubercles or pus is obtained, according to the animal experimented upon or the mode of introduction.

Of all accidental pyogenic microbes the most interesting is that of typhoid fever. Numerous experimental researches have demonstrated that this microbe can produce abscesses in animals. The pure bacillus of Eberth has been met with in a certain number of suppurative lesions consecutive to typhoid fever. Dehu, in his thesis (1893), collected forty observations. According to Chantemesse and Widal, these suppurations are most frequently observed in the bones; then, in order of decreasing frequency, in the meninges, pleura, peritoneum, and synovial membrane. The thyroid and the testicles are the two glands in which it is not infrequently localized. The spleen is the only viscus in which such process has been noted. The course is at times acute, but more frequently its evolution is slow. In the latter instance we have to deal with cold suppurations. Such is the case particularly in osteomyelitis with successive exacerbations, which are prolonged for years, and the same is true in tuberculous osteitis. These facts should be remembered, as they are not extremely rare. Their complete history will be found in the work of Chantemesse and Widal.[1]

4. Vegetable Pyogenic Parasites.

Several species of streptothrix or oöspora are capable of producing suppuration in man and animals. The most important is incontestably the *oöspora asteroides*, discovered by Eppinger in a case of meningitis and again found under analogous conditions by Almquist. The same parasite has been seen by Ferre and Faguet in a cerebral abscess; by Sabrazes and Riviere in the sputa of a patient, in the

[1] Chantemesse and Widal. Des suppurations froides consécutive à la fièvre typhoïde. Société médicale des hôpitaux, November 24, 1893.

pus of subcutaneous abscesses, and in abscesses of the brain and kidney. We will again refer to the group of oöspora in treating of actinomycosis.

Special mention is due to a mucor found by Paltauf in a patient suffering from a strange affection characterized by pharyngolaryngeal phlegmon, pneumonia, and intestinal ulcerations. The parasite that had given rise to these various lesions was analogous to the mucor corymbifer whose pathogenic action upon animals was first shown by Lichtheim.

The pathogenic properties of yeasts and of oidium albicans will be discussed in a special chapter.

Finally, more highly organized parasites, such as the tricophytons, may also induce suppurations. Rosenbach admits seven pyogenic species of them, among which the most important are the *T. mentagrophytes* in man and in the horse, and the *T. felineum* in the cat and in children.

It is well to add that the majority of pyogenic plants are capable of producing infectious nodules comparable to tuberculous granulations. Such is the case with regard to the mucorinæ, the aspergillus, the saccharomycetes, and the oidium. These various parasites will again be referred to in the chapter on pseudotuberculoses. Some of them may even produce genuine tumor. It will suffice to mention the actinomyces. Here, then, we have to deal with a series of facts which establish numerous transitions between lesions seemingly very widely apart—suppurations, granulations, and neoplasms.

5. Pyogenic Animal Parasites.

The study of diseases suffered by inferior animals has drawn the attention of observers to the pathogenic rôle of the protozoa. The presence of infusoria and flagellatæ in the suppurations occurring in man has long been noted. The *balantidium coli*, for instance, in the suppurative lesions of the intestine; the *trichomonas vaginalis* in vaginal suppurations and in chronic affections of the digestive canal. It may well be questioned, however, whether these parasites are not accidental guests by no means pathogenic.

The *ameba coli*, an animal parasite, is held by many observers to be the agent of one of the clinical types of dysentery. What is of more direct interest for our subject is the fact that this parasite is at times found unassociated with other organisms in hepatic abscesses consecutive to dysentery. With Dr. Peyrot, the author

observed a case of this kind. It is a question, however, whether the pus did not at some time contain pyogenic bacteria which had disappeared. The interesting experiments of Marchoux seem to establish that the ameba of dysentery is really capable of creating suppuration.

Relative Frequency of the Various Pyogenic Agents.

Among the pyogenic microbes above described the most widely distributed are the staphylococci and the streptococci. It is not rare, however, to find several bacteria together in the same focus. Ogston studied sixty-nine abscesses and detected the simultaneous presence of two species in sixteen instances. Zuckermann found records of 495 bacteriological examinations of hot abscesses. In 70 per cent. of the cases the staphylococcus had been found; in 16 per cent. the streptococcus, and in 5.5 per cent. both of these species. Then followed the *bacillus pyogenes fetidus*, the *bacillus pyogenes tenuis*, the tetragenus, etc.

The association of several pyogenic microbes seems to result in an aggravation of the suppurative phenomena. Suppose two pyogenic microbes attenuated to such an extent that each, injected alone, produces no disturbance. If they are united, the result of their simultaneous inoculation is the formation of an abscess.

By mixing a harmless sample of the staphylococcus with a saprophyte or an attenuated culture of streptococcus, suppuration is obtained. By study of the purulent focus, however, Trombetta recognized that the focus soon became monomicrobic. The staphylococcus prevailed, and soon no other microbe was discoverable. This fact is in harmony with the findings of clinical observation. A focus may at first contain one pyogenic species, and at the end of a certain period of time, another. Such is particularly the case in otitis. Whatever may have been the microbe found at the beginning the staphylococcus is almost always found at a later period. Thus, there are microbes which start a suppuration and microbes which maintain it. If it be further remembered that simple saprophytes play an auxiliary rôle in the production of suppurative phenomena, it will readily be understood why all purulent foci should be protected against external germs, even apparently inoffensive ones.

The true pyogenic microbes, notably the staphylococcus and the *B. coli*, are abundantly distributed in nature, but are epiphytes rather than inhabitants of the inorganic world. They are, therefore,

found mostly in crowded neighborhoods, in hospital wards, and in water polluted by men and animals. Once thrown into the external world, these pyogenics would soon destroy each other if they were not protected by the organic materials in which they reside. Pus, mucus, fecal matter, etc., shield them against causes of destruction, especially against the influence of the sun. These facts must be taken into serious account, since in experiments it is the resistance of pyogenic germs derived from cultures, and, consequently, placed under less favorable conditions, that is studied. When they resist cosmic agents and struggle for life against other microbes, the pyogenics gradually lose their aptitude to thrive in living organisms, become attenuated, and finally assume the rank of simple saprophytes. This is what happens, for instance, with the streptococcus.

The staphylococcus aureus has been detected in the air (Fraenkel), dust, soil (Lubbert), and water (Ullmann). It seems to be more resistant than the streptococcus. The latter cannot live more than five days in sewer water, while the former is still living at the end of twenty days (Strauss and Dubarry), or even several months (Meade Bolton). The tetragenus resists eighteen to twenty days. The author has several times found this microbe in the air, a fact well in harmony with its frequent presence in the buccal cavity.

The pneumococcus is far more delicate than the preceding microbes. Except when it is protected by the mucus of expectorations, it becomes attenuated and soon perishes.

The *proteus vulgaris* and *mirabilis* and, above all, the *bacillus coli* are also among those pyogenics which are frequently found outside the organism. The last-named microbe is widely distributed and can vegetate in water for months.

These microbes, though capable of living in the external world, are nevertheless parasites, and are mostly found in man and animals. The *S. aureus* normally vegetates on the skin. It may also be met with in the mouth and in the nasal mucus. Escherich has detected it in the stools of healthy children, a result due to contamination of the mother's milk at the nipple. The author always found the *S. albus* in milk taken under ordinary conditions, while this secretion was found to be sterile when obtained with necessary precautions.

Streptococci may be detected in the same localities as staphylococci, but the former are inclined to abandon the exposed parts of the organism. They are seldom encountered in the skin. Their

seat of predilection is the buccopharyngeal cavity, where they are constantly present. They may invade the digestive tract and the genital organs of women in the lower part of the vaginal canal. This last localization explains their frequency in the lochia of women in nowise infected.

The tetragenus and pneumococcus are likewise found in the mouth. The pneumococcus is met with in about one-fifth of all subjects. No wonder, therefore, that the inoculation of saliva into the rabbit, and especially the mouse, may give rise to a speedily fatal septicemia. The infection thus produced, which was discovered by Pasteur and well studied by Sternberg, is due, as the researches of Fraenkel have established, to the agent of fibrinous pneumonia.

The *B. coli* is also widely distributed from the mouth to the anus, whence it enters the genital organs. It is also found in all animals. Hence its constant presence in milk. In fact, the researches of Wurtz and Leudet tend to establish that the lactic ferment is nothing else than a variety of colon bacillus.

From this brief exposition, it may be seen that the pyogenic microbes are everywhere within and external to our bodies. This fact points to a rather restricted action of microbes and re-establishes the rôle of the organism in the development of morbid phenomena.

We are thus led to consider how and why the pyogenic microbes invade the human organism and how they, at times, become virulent.

Auxiliary Causes of Suppuration.

The mode of development of a suppuration is easily accounted for when the process is induced, not by microbes which we habitually harbor, but by exalted germs of diseased animals and men. The question, then, is to learn how this primary focus, which directly or indirectly contaminates other individuals, originated. In many cases suppuration is the result of a traumatism which, producing a solution of continuity, offers an entrance to these microbes. The latter find a favorable medium in the altered tissues and rapidly develop.

It must be recognized, however, that traumatism does not always suffice to give rise to suppuration, even in the absence of antiseptic precautions. The experiments of Garré, Schimmelbusch, and Washmuth established that pyogenic micro-organisms can penetrate into the skin of man and animals in the absence of the slightest cutaneous abrasion.

At the present day it is a matter of common knowledge that a

pyogenic microbe introduced into the organism does not necessarily give rise to symptoms. It may be rapidly destroyed. If, in other cases, it succeeds in doing mischief, it is owing to a series of secondary causes, some of which depend upon the microbe, others upon the invaded organism.

On the part of the microbe we have to count with the number, virulence, and mode of introduction. Fehleisen long since recognized that small amounts of staphylococci and streptococci may be injected beneath the skin without producing any lesion. To produce an abscess he had to employ 1 c.cm. of the culture. If 5 c.cm. were introduced, the animal died in eighteen or thirty hours without any suppurative manifestation. According to Odo Bujwid, suppuration does not appear when 1,000,000,000 staphylococci are injected into the rabbit, the rat, or the mouse. It may happen that even 8,000,000,000 are insufficient for the rabbit, while this amount is always fatal for the rat.

The value of these figures should not be exaggerated. The results evidently depend upon the degree of virulence of a given sample, since it has long since been well known that microbes possess no fixed, definite potency. When pyogenic microbes are of moderate virulence, they produce pus; when highly exalted, their inoculation causes general infection, and the animal speedily succumbs to septicemia, and microscopic examination reveals no appreciable lesions in the cadaver. On the other hand, when they are too attenuated, they often prove incapable of giving rise to the slightest lesion, even though they are introduced in considerable numbers. The results vary not only with the number and the degree of virulence of the microbes, but also with the mode of entrance. Experimenting upon rabbits, Herman discovered, for instance, that the peritoneum is twenty times more resistant than other parts to inoculations of staphylococcus.

When directly injected into the blood, the pyogenic microbes become localized in various organs and there produce purulent foci. These localizations may be favored by visceral lesions. If, for instance, the cardiac valves are the seat of traumatism, an ulcerative endocarditis is obtained; if a fracture has been produced, the result will be an osseous suppuration. It is possible to thus create artificially points of fixation for the agents in circulation. Inspired by this fact, Dr. Fochier attempted to create aseptic foci designated by the name of abscesses of fixation. In his opinion, these foci were

calculated to attract the microbes to those points where they would do little, if any, harm to the organism.

Tissues in active growth may likewise represent points of attraction for agents in circulation. Intravenous injection of pyogenic microbes may induce osteomyelitis in young animals, as has been shown by Rodet experimenting with the staphylococcus, and by Courmont and Jaboulay, and Lannelonge and Achard with the streptococcus.

Role of Nervous Alterations. Simple section of the sciatic nerve, without inoculation of microbes beneath the skin, is not followed by trophic ulcerations, at least in the rabbit. Such is not the case with the guinea-pig. In this animal a gangrenous edema of the lower segments of the limb of the operated side supervenes some time after the excision of the nerve. The tissues swell and are infiltrated with pus, then disintegrate and leave the skeleton denuded. The animal finally dies. The fact is that the ulcerations produced by the wound upon the surface of the skin served as portals of entrance to the microbes, and the germs rapidly multiplied in those tissues whose vitality was diminished and gave rise to extended injury.

The sciatic is a mixed nerve—motor, sensory, and vasomotor—and certain of its fibres seem to have antagonistic actions upon a local infection. In order to prove the rôle devolved upon the various parts of the nervous system, it was necessary to operate upon nerves performing a special function. I therefore first studied the influence of the sympathetic nerve.

Brown-Séquard long since had established experimentally that section of the great sympathetic favored the healing of wounds. Operating upon rabbits, the author introduced from six to seven drops of a streptococcus culture into the two ears at the same point —*i. e.*, in the middle portion, a little to the inside of the central artery. Immediately after the inoculation the author extirpated the superior cervical ganglion on one side. At the end of twenty-four hours the operated ear was found hot and infiltrated with serum. The inflammation increased and reached its maximum toward the third or fifth day. From this moment onward the aspect of the two ears completely changed. On the operated side the lesions resolved; on the intact side they were aggravated. Toward the sixth or eighth day the nerveless ear resumed its normal appearance, while on the intact side the lesions grew worse, infiltration being enormous, abscesses and phlyctenulæ having developed, as a result of which a

part of the ear sloughed and perished. The edematous infiltration generally disappeared toward the fifteenth day, persisting, in some instances, for twenty and even fifty days.

In these comparative experiments section of the sympathetic nerve produces a double effect. It gives rise to congestion in the operated ear, and to anemia in the intact ear. The results thus become extremely clear owing to the production of contrary vasomotor modifications on the two sides.

These experimental facts remind us of certain clinical observations. It is well known that heat is employed to heal certain suppurative inflammations. Active congestion, whether produced by hot applications or by vasomotor dilatation of the arteries, favors recovery. It may, therefore, be concluded that active congestion is favorable to the healing of a local lesion, while passive congestion renders such lesion more serious and tends to produce gangrene. Similarly, in a cardiac patient in the stage of asystole, the slightest lesion results in suppuration or sphacelation. Finally, suppression or diminution of the blood supply, as is realized by ligation of arteries, favors the development of local lesions.

The influence of sensory nerves upon the development of suppuration can easily be demonstrated by sectioning the auriculocervical nerve of a rabbit and injecting streptococci beneath the skin of both ears. In order to obtain clear results, use should be made of an agent of moderate power which gives rise only to a small, circumscribed abscess on the intact side. The ear deprived of the nerve becomes the seat of an intense lesion—*i. e.*, a very marked edema, phlyctenulæ filled with a serous fluid, and abscesses, which may result in mutilation or perforation of the organ.

Role of Previous Local Lesions. The presence of foreign bodies in a wound exercises a harmful influence upon the evolution of the process. This fact is one of those proved beyond all doubt by clinical observation. In many cases the seemingly endless process of suppuration has been abruptly stopped by the extraction of a piece of cloth, a fragment of a bullet, or a splinter.

The harmful influence of caustic or irritant substances upon inflammatory processes is more marked. The author has tried, with Dr. Josué, the effect of trimethylamin and of carbolic acid. With an amount of colon bacillus sufficient to produce only a small abscess in the controls, half a gram of trimethylamin was injected beneath the skin of the thigh of a rabbit. The result was a phlegmon invad-

ing the cellular tissue of the abdomen. The effect of carbolic acid is even more manifest. This antiseptic substance, far from combating infection and preventing suppuration, favors them. Having injected subcutaneously, as above, a solution of 5 cg. of carbolic acid in 1 c.cm. of water, then 0.5 c.cm. of a culture of colon bacillus in bouillon, we noticed the production of an enormous diffuse phlegmon infiltrating the whole thigh and the lower half of the abdomen. If, however, only 2 cg. of carbolic acid is injected, no result whatever is obtained. This is a fresh demonstration of the harmful action of strong antiseptics.

This noxious influence of chemical substances upon the vitality of tissues is equally exercised by disease. The tissues already altered by a morbid process are exposed to the invasion of pyogenic microbes. It will suffice to remember the purulent foci developing in neoplasms or in the lungs during a pneumonia or tuberculosis. The importance of these secondary infections is well known, as they play a considerable rôle in the production of cavities and explain the hectic phenomena observed in the third stage of consumption.

Influence of the General State. Individual predisposition and resistance largely depend upon the general state of the organism. It is an undoubted fact that suppuration is more liable to develop in certain subjects than in others. The slightest abrasion in them occasions an abscess or a phlegmon. Even without any solution of continuity, a contusion or friction suffices to permit the penetration of germs. In other cases, in the absence of any appreciable cause, cutaneous suppurations, acne, abscesses, furuncles, and anthrax appear, and sometimes repeatedly.

These transitory or permanent predispositions depend upon either a diathetic condition, an inherited or acquired mode of nutrition, or a series of causes the influence of which has been conclusively established by numerous clinical and experimental facts. Such are overwork, exposure to cold and heat, starvation, cachexias, and, above all, intoxications.

We have an interesting illustration of this fact in mercurial stomatitis. The buccal lesions are not due to the elimination of mercury. On the contrary, the mercury acts by creating a morbid predisposition and by diminishing the resistance of the tissues. Hence, the rapid development of pyogenic microbes and the exaltation of their virulence, which explains why mercurial stomatitis may become contagious. Diday reported the history of a man who communicated

this affection to his wife. Transmission of exalted bacteria had occurred in this case.

The cutaneous manifestations of bromism and iodism are likewise accounted for by the development of pyogenic microbes present upon the surface. The phenomena are, however, more complex in this instance, as the concomitant gastrointestinal disturbances must also be taken into account. In fact, Dr. Féré has established that these infectious manifestations may be diminished and suppressed by means of intestinal antisepsis.

Those chemical substances which diminish the alkalinity of the blood seem to favor suppuration; but the results are not sufficiently conclusive. On the other hand, some authorities maintain, though their conclusions have often been contradicted, that the administration of sodium bicarbonate for some length of time renders the animals more resistant by increasing the alkalinity of their humors.

There is a group of substances which favor the development of pyogenic agents. We refer to ferments. The author has shown that the attenuated streptococcus recovers its virulence when it is injected with papain. What the products of highly organized plants do, microbic products, ferments, and ptomains can also realize, and even more readily. Grawitz has thus recognized that the simultaneous introduction of cadaverin and staphylococci or streptococci gives rise to a violent phlegmon, the alkaloid and the microbe having powerfully aided each other.

The resistance of the organism to pyogenics also diminishes as a result of nutritive disturbances suffered in grave diseases. Convalescents from typhoid fever, for instance, often develop manifold suppurations, abscesses, and furuncles, which may adequately be accounted for by insufficient nutrition of the subject.

Finally, it is interesting to note that quantitative modifications of the blood seem to be without influence. Even abundant and repeated general bleeding is ineffective.

Generalization of Suppurating Lesions.

We have thus far studied the causes which explain the development or aggravation of a purulent focus. It is evident, however, that suppuration does not always remain circumscribed, and that the microbes may emigrate and give rise to visceral colonies. Why are not the germs which enter the circulation destroyed by the protective organs? Rinne justly attributes this failure to a general

decline of the organism, due to the effect of microbic products originated at the primary focus. As microbic secretions vary with the samples employed and the aptitude of the organism to neutralize the toxins differs from one individual to another, it is readily conceived why the process sometimes remains local and at others becomes generalized.

Of the microbes which pass into the general circulation, some are destroyed by the leucocytes, some are eliminated, and others remain in the tissues. The elimination is mainly effected by the kidneys and the skin. Brunner, Eiselsberg, Gaertner, Tizzoni, Preto, Nannotti, and Baciocchi have detected the staphylococcus in the urine and sweat in cases of general infections, even in benign suppurations. The latter instance is of great interest, as it tends to prove that pyogenic microbes easily penetrate into the organism, but are quickly destroyed or eliminated. Elimination through the emunctories seems to be achieved without any inconvenience to the eliminating organs. It is a true, natural, therapeutic procedure.

Such is not always the course of events, however. The microbes that have found access to the organism are not invariably destroyed or eliminated, and, if very virulent, they then are capable of causing a fatal septicemia. If they are less active they create purulent foci, which, according to their number and locality, may resolve or prove fatal. The formation of visceral foci may, therefore, be considered as a last defensive measure on the part of the organism. Numerous clinical facts demonstrate that in puerperal women, for example, the development of a phlebitis or of a periuterine phlegmon coincides with amelioration of the puerperal fever and a retrogression of alarming phenomena. The localization may become very grave of itself, but the immediate accidents are, in part, avoided.

Non-microbic Suppurations.

We have seen that most of the known microbes may, under certain circumstances, give rise to the formation of a purulent focus. We now come to the question whether suppuration is ever possible without the intervention of animate agents. Hueter and his disciples were the first to experiment with aseptic substances by injecting a certain amount of a solution of silver nitrate and of zinc chloride into the subcutaneous cellular tissue. No abscess followed, and the authors concluded that there is no pus without microbes.

In 1883 Straus published the result of forty experiments made upon rabbits, guinea-pigs, and rats. He had introduced beneath the skin the most varied substances, such as croton oil, sterilized water, mercury, etc., and in no case did he observe suppuration, save when microbes had accidentally penetrated. Analogous results were obtained by other experimenters. In 1885 the Medical Faculty of Berlin made this a competitive question. Klemperer secured the prize. In his various experiments intense inflammation, or serous exudation, or even coagulation necrosis was observed, but there was no pus. Zuckermann experimented with no less than thirty-one substances, and never observed pus without microbes.

So many experiments performed by able scientists would seem sufficient to settle the question, but we shall now cite another series of researches leading to a diametrically opposite conclusion. Riedel obtained aseptic suppuration by injecting mercury into the knee-joint of a rabbit, and Cohnheim, by introducing croton oil beneath the skin of a dog. Councilman took up the question and resorted to a very ingenious procedure. The substance under study was placed in a glass tube which was then closed at both ends. The tube was inserted beneath the skin of the animal and was broken when the small wound had cicatrized. By this method, the employment of a mixture of croton oil and olive oil produced pus in the rabbit without any micro-organisms.

We owe one of the best works on this subject to Grawitz and Bary. These authors demonstrated that it is hardly possible to produce in rabbits and guinea-pigs suppuration without microbes. The case is different with the dog. A 5 per cent. solution of silver nitrate and concentrated ammonia were found capable of giving rise to aseptic abscess. Terebinthine is, however, the substance endowed with the most marked pyogenic properties. Nathan failed to prove this action owing to the insufficient amount (0.6 c.cm.) employed by him.

As has well been remarked by Rosenbach, the fundamental shortcoming of the first experimenters is the generalization of the results obtained with one animal species. Various substances, particularly mercury and terebinthine, are pyogenie for the dog, while they are only phlogogenic for the rabbit and the guinea-pig. Other experimenters subsequently confirmed this distinction.

The problem may now be held to have been solved. In the absence of microbic intervention, suppurations may develop by the action of chemical substances. The list of such substances has been con-

siderably augmented by the latest contributions upon this subject. The higher the dose and the greater the concentration of these substances, the more energetic is their action. Hence, the possibility of varying their effects so as to obtain a simple serosanguinolent exudate, an abscess, a phlegmon, or a slough.

Researches have further demonstrated that the character of pus of chemical origin is the same as that of pus of bacterial origin.[1]

Lastly, Poliakoff has discovered the very interesting fact that the more slowly the pyogenic chemical substances are introduced into the tissues, the better they act. To demonstrate this, he introduced small capsules of collodion containing five drops of turpentine oil beneath the skin of a rabbit. A large abscess was produced, although only a part of the amount introduced had had time to diffuse. The counterexperiment consisted in injecting five drops at once. The result was slight tumefaction without suppuration.

Pyogenic Properties of Microbic Products. Researches pursued by a number of authorities have demonstrated that subcutaneous inoculation of sterilized cultures of bacteria may give rise to suppuration. This action is in part due to bacterial protoplasm and in part to soluble substances.

A great number of experiments have shown the presence of pyogenic material among the secretory products of the *staphylococcus aureus*. Leber has succeeded in extracting from its cultures a crystallizable body, soluble in alcohol, and possessing inflammatory and necrosing power in the highest degree. The author designates it under the name *phlogosin* and distinguishes it from the non-toxic alkaloids found by Brieger in pus. No analytical study has been undertaken related to substances in cultures of other pyogenic microbes.

The Non-microbic Suppurations in Clinical Observations. It was for some time believed that the study of non-microbic suppurations was only of theoretical interest. It is at present known that non-microbic suppurations may also occur in man. The pus in chronic salpingites often contains no bacteria. The same is true as regards hepatic abscesses, as has been pointed out by Kartulis, Laveran, Netter, and Peyrot. Since these first contributions thirty-eight observations have been published concerning non-microbic suppurations of the liver.[2] Brouardel and Josué have reported the observa-

[1] Poliakoff. Ueber Eiterung mit und ohne Mikroorganismen. Centralb. f. Bakt., Bd. xviii. p. 33, 1895.

[2] Longuet. La stérilité dans le pus des abcès du foie. La Presse méd., 1895, p. 99.

tion of a cerebral abscess in which the pus was free from microbes. Tuffier, operating upon a calculopyelonephritis, found a litre of fetid pus containing no bacteria cultivable by the ordinary procedures. In the majority of instances in which suppuration is sterile, the purulent focus gives rise to no notable disturbance and arouses no general reaction.

Several hypotheses have been advanced to explain the aseptic character of certain purulent foci. Only one seems to the author acceptable. The probabilities are, to say the least, that the focus has primarily been fertile—viz., that it developed under the influence of the ordinary pyogenic germs, which subsequently disappeared. This view is supported by certain clinical and experimental facts. The author has reported two such experiments pursued with Dr. Josué. Half a cubic centimetre of a culture of proteus vulgaris was injected into the cellular tissue of the thigh of a rabbit. A month later the animal was killed. The necropsy revealed a circumscribed abscess the size of an almond. The pus of this abscess contained no microbes visible under the microscope. It produced no growth in the various artificial culture media. Inoculated into the cellular tissue of a rabbit, it caused no lesion. The second experiment was made upon a rabbit with *B. coli* with analogous results.

It may be concluded, therefore, that when a suppuration is produced in an animal in such a manner as to allow no communication with the external air, the microbes introduced become gradually attenuated, are no longer cultivable, and can no longer overcome the resistance opposed to them by the living organism. Diminution and disappearance of virulence, diminution and disappearance of vegetability, degeneration and dissolution are the successive phases through which pyogenic microbes pass in a closed focus.

Physical and Chemical Characters of Pus. The characters of pus vary notably from one sample to another. Phlegmonous pus, which is always taken as typical, is an opaque, creamy, yellowish-white, odorless fluid. On ebullition, it smells like milk. Its taste is rather sweet, which is due to the presence of a great amount of soap masking the salty flavor of sodium chloride.

Under certain circumstances pus occurs as a thick mass, resembling certain soft cheeses. Such caseous pus is frequent in animals, particularly in small rodents, such as rabbits and guinea-pigs, employed in laboratories. In other cases, pus is thin. The serous portion is partially separated from the solid elements which are found

in the form of coagula. It is often contaminated with products of putrid fermentations. It then becomes sanious, gangrenous, of a chocolate-brown color, and contains detritus of necrotic tissue, at times gas, and exhales a nauseating odor.

Rosenbach supposed that the color of pus was related to the nature of the pyogenic agent—that the staphylococcus aureus was concerned in the formation of yellow pus, and that the S. albus was found in the white variety. This idea does not seem to be correct, and we need not wonder, since the S. aureus produces no pigment when it is protected from air, as is the case with foci of suppuration.

It is not practicable, therefore, to determine, by examining a sample of pus, what pyogenic agent is concerned, or to tell whether the pus is actually inhabited by living microbes or is free from bacteria. Cultures are indispensable. An exception may be made only with suppurations caused by the pneumococcus. These are remarkable for their thickness, due to the great amount of fibrin present, and for their greenish color. Hence, the possibility to declare their origin at first sight.

Microscopic examination may reveal the origin of a suppuration by the various elements present, such as glandular cells, fibres of connective or elastic tissue, crystals of fatty acids, cholesterin, hematoidin, calcareous grains, and, finally, microbes.

Certain pathological secretions resemble pus. Such, especially, is the concrete mucus found in endometritis; then the steatomatous fluid of sebaceous cysts and, to a certain extent, the contents of syphilitic gummata. Error in these cases may easily be avoided. However, the chyliform exudates of serous membranes, notably in the pleura, peritoneum, and tunica vaginalis, have long been mistaken for pus. These are probably cases of old purulent foci in which the morphological elements, microbes, and animal cells have undergone fatty degeneration. There remains only an emulsion of fat, the nature of which may readily be determined by microscopic examination or chemical analysis.

In genuine pus the microscope reveals the presence of characteristic cells, formerly designated as pyocytes. It is at present possible to differentiate the cells and, in fact, the same elements are found in pus as in the blood. Pus contains polynuclear neutrophile, eosinophile, and, exceptionally, basophile leucocytes, as well as mononuclears and lymphocytes. Finally, there are found two orders of degenerated cells: the so-called corpuscles of Gluge, which seem to

be made up of an agglomeration of disintegrated cells, having undergone fatty degeneration, and, in the next place, large spheroidal cells, often in a state of mucoid degeneration, and derived from the fixed cells of connective tissue and from endothelial or adipose cells.

These various cellular elements are found in variable proportions. The polynuclear neutrophiles predominate in ordinary pus. Gonorrheal pus is said to be remarkable for the great abundance of eosinophiles it contains. In reality, however, these cells abound only at the time when the acute phenomena are subsiding. Their appearance is always an indication of recovery. It may be hoped that further advances in the cytological study of pus will furnish data utilizable in clinical observation. Not that the cellular formulæ vary with each species of microbe; on the contrary, they seem to be related rather to certain groups of pathogenic agents. Thus the pus produced by microbes so closely related as are those of variola, varicella, and vaccinia, possesses the same character. In all three instances it is remarkable for the abundance of mononuclears it contains.

Chemical Characters of Pus. From what has been said regarding varieties of suppuration, it is natural to conclude that pus does not always possess the same chemical characters. The results obtained by analyses cannot, therefore, have a general bearing. They nevertheless deserve to be examined in detail.

Pus is a neutral fluid, at times alkaline, seldom acid. Acidity, when present, is due to fatty acids and notably to butyric acid.

Treated with nitric acid, pus gives an abundant precipitate of albumin. The addition of ammonia transforms it into a semisolid, translucent mass, similar to thick mucus. This effect is referable to the action exercised upon the albumin by the leucocytes destroyed by the alkali.

The specific gravity of pus varies from 1020 to 1040. With phlegmonous pus it varies between 1031 and 1033. When left to itself, pus does not coagulate, because it contains no fibrin. When heated, it solidifies at about 167 F. (75 C.). Allowed to stand, pus separates into two layers: a clear, superficial layer, the pus serum, and a lower opaque layer, which contains the cellular elements, the pyocytes. There are 710 to 831 parts of serum to 166 to 290 parts of corpuscles. These figures are variable.[1] The chemical analysis of pus corpuscles, made by Hoppe-Seyler, gives the following figures:

[1] Ch. Robin. Lecons sur les humeurs normales et morbides du corps de l'homme. Paris, 1874, 2d ed., p. 376.

ORGANIC SUBSTANCES CONTAINED IN ONE HUNDRED PARTS OF DRY CELLS.

	I.		II.	
Proteids	13,762	68,585		67,369
Nuclein	34,257			
Insoluble substances	20,566			
Lecitin	14,383		7,564	
Fat			7,500	
Cholesterin	7,400			7,283
Cerebrin	5,199		10,284	
Extractive substances	4,433			

INORGANIC SUBSTANCES CONTAINED IN ONE HUNDRED PARTS OF DRY CELLS.

NaCl	0.435
$Ca_3(PhO_4)_2$	0.205
$Mg_3(PhO_4)_2$	0.113
$Fe_2(PhO_4)_2$	0.106
PhO_4	0.916
Na	0.068
K	traces

The pus serum resembles blood serum in its chemical constitution. Some authorities have even gone so far as to regard the two fluids as identical. It has been objected that the composition of pus serum is not constant, but the blood serum is no less variable. This is clearly demonstrated by the following figures:

	Serum of Blood (C. Schmidt).		*Serum of Pus (Hoppe-Seyler).*	
	I.	II.	I.	II.
Water	917.15	908.84	913.70	905.65
Organic substances	74.43	82.59	78.57	86.58
Inorganic substances	8.42	8.57	7.73	7.77

Among the substances found in pus serum the most important are undoubtedly the albuminoids, serin, globulin, albumose, and, in osseous abscesses, chondrin. Much stress has recently been laid upon the presence of ferments, toxalbumins, and ptomains, depending in part upon the multiplication of microbes. Dr. Achalme, who has made an admirable study of ferments contained in pus, notes the presence of lipase, amylase, trypsin, casease, a zymase liquefying gelatin, another decomposing peroxide of hydrogen, and, finally, oxidase. The last-named ferment is always very abundant. Sucrase inulase, emulsin, lactase, and plasmase are always absent. These various ferments are not produced by microbes, since they are also found in aseptic abscesses. Dr. Achalme is inclined to assign their origin in the leucocytes.

Development and Evolution of Purulent Foci.

Suppuration cannot, in the author's opinion, be held to be a reaction aroused directly by chemical or animate pyogenic agents. The mechanism is more complex, and involves two distinct acts. The pyogenic agents first give rise to a necrosis, a primary mortification of tissues. The parts thus altered become a cause of secondary irritation which is expressed by the production of round cells, of which some originate on the spot and others migrate from the vessels.

When pyogenic toxins or a chemical substance, like turpentine, are introduced into the subcutaneous cellular tissue, the first act of pyogenesis is, as has been shown by Bardenheuer with turpentine, a cellular necrosis. A reaction then becomes manifest. This is the second act of the process. Around the necrosed region the cells swell and proliferate. At the same time the vessels dilate and exude a serosity, while the leucocytes migrate from the blood current and take up a position between the necrosed and the inflamed parts. Some of the new cells, however, die and remain in the central zone of the focus. We may admit, then, with Lemiere, that, as a rule, every suppurative focus consists of three zones: a central necrosed zone; a middle zone, characterized by an infiltration of leucocytes, and a peripheral zone made up of fixed cells which proliferate and tend to encyst the lesions.

Among these phenomena the arrival of leucocytes is a most interesting one. It is known that the blood normally contains about 6000 leucocytes per cubic millimetre, or 30,000,000,000 for the five kilograms of blood of the human body. In phlegmonous pus 125,000 pyocytes per cubic millimetre are counted, or 125,000,000,000 per kilogram (one litre). In some cases suppuration amounts to 500 or even 1000 c.cm. in twenty-four hours. Taking the lesser figure, 500 c.cm., we see that the focus discharges 60,000,000,000 round cells, the greater part of which is represented by leucocytes. This is nearly twice as much as the number of leucocytes contained in the total amount of blood. It is to be noted that the phenomena of diapedesis are prepared and preceded by an increased leucocytosis. The blood of an individual suffering from suppuration is found to contain 15,000 to 20,000 leucocytes per cubic millimetre; in some cases this figure reaches 36,000.

It now remains for us to learn how this increased production of white corpuscles is effected. It probably depends upon the microbic

and cellular secretions occurring in the focus of suppuration. In fact, it has been established that the secretions of certain microbes and the proteins contained in their protoplasm excite leucocytosis (Buchner). In non-microbic suppurations this rôle of excitant must devolve on the products of cellular destruction.

The microbic or cellular products thus originating in the affected parts act probably upon the organs in which the leucocytes are formed—the bone-marrow, lymphatic glands, spleen, and, in children, the thymus. They induce proliferation in distant parts as they do in the main focus. Nutritive and proliferative overactivity may, perhaps, account in part for the fever of suppuration.

Cohnheim had already noted that the leucocytes could not emigrate unless the vessels were dilated and the circulation slowed. After these white corpuscles have passed out of the bloodvessels, they make their way to the pyogenic agents. In fact, it has been demonstrated that sterilized cultures of the *staphylococcus aureus* possess the property of attracting the migrating cells. If a number of capillary tubes be introduced into the abdomen of a frog, some of the tubes being filled with sterilized cultures of the microbe mentioned and others with water or bouillon, the latter remain untouched, while the former become filled with numberless leucocytes. The products of organic disassimilation exercise an analogous influence and, consequently, the cells altered by pyogenic substances become a new source of attraction for the leucocytes.

Some of these leucocytes, when in contact with the accumulated products in the foci, undergo rapid necrosis. Others, simply irritated, proliferate by direct division of the nucleus. While the migrated leucocytes are at work the fixed cells of the tissue do not remain inactive. The old experiments of Hoffmann and von Recklinghausen tend to prove this. These authors irritated the cornea of an animal and then placed the eye or the entire head in a damp chamber. After some time they found an accumulation of round cells at the irritated point. Von Recklinghausen has likewise seen the cells of the cornea undergo a change in form and become migrating cells. Similar modifications have been described in the cells of connective and adipose tissue, and in those of serous membranes (Cornil and Toupet). According to Grawitz, connective tissue cells are the seat of an active karyokinesis and are transformed into mononuclear and even polynuclear corpuscles. Let us also recall the recent researches of Ranvier on the clasmatocytes, those large connective tissue cells

which represent fixed leucocytes and, under the influence of inflammation, are again converted into white corpuscles.

The respective rôles of fixed and wandering cells have been shown by the researches pursued by Ribbert with the staphylococcus, and by Kiener and Duclert with the tetragenus.

A focus of necrosis is first produced, then large leucocytes enter the field, which process takes place coincidently with a proliferation of fixed cells. These various cells are endowed with great phagocytic activity. Such are the phenomena observed on the first day. On the second day the fixed cells become the seat of karyokinesis and begin the process of repair. At this time leucocytes of the smaller variety arrive. If, however, the quantity of microbes introduced is quite considerable, many phagocytes die, and some of them, as well as the microbes yet at large, are seized and ingested by the macrophages—*i. e.*, by the large mononuclear cells derived from the connective tissue cells. The phagocytic rôle of fixed cells is especially marked from the fourth day onward. At this period the enveloping or pyogenic membrane becomes vascularized, granulations develop rich in giant cells, which continue the work of phagocytosis, and in white cells, which become the future clasmatocytes.

According to Ribbert, the round cells defend the organism not only by ingesting the microbes, but by forming a barrier around the virulent focus and establishing a sort of vital competition with the pathogenic agents. The latter succumb because their supply of nutrient elements and oxygen is cut off and they are poisoned by their own noxious substances.

Thus, while on the one hand the microbes are ingested and destroyed, on the other the cells die. If the dead cells are not very numerous, the macrophages pick them up and remove them as well as the bacteria contained in them (scavengers). No suppuration is produced and, after a certain time, the lesion is completely healed. If, on the contrary, the number of dead cells is considerable, the cadavers accumulate in the focus, and thus is constituted the purulent collection.

In most cases the abscess opens externally, and the dead elements with a great number of microbes are thus expelled. Nevertheless, virulent agents remain in the focus, and it may be asked how a cure is ever possible, especially when the purulent focus becomes encysted. In such cases, the author believes a chemical modification of the fluids and tissues of the organism takes place, rendering the media

unfavorable for the development of the microbes. The vitality of the latter gradually declines, and their removal by phagocytes is easily accomplished. If the focus remains closed, cure is possible, but the pus then undergoes transformations. In some instances the elements of which it is composed undergo fatty degeneration, so that the focus is transformed into a chyliform fluid. In other cases, the serum is absorbed and there remains a caseous mass which may later become infiltrated with calcareous salts.

The suppurative process is attended by local and general symptoms. The local symptoms are well known as the four cardinal signs of inflammation—swelling, pain, heat, and redness (tumor, dolor, color et ruber). The primary phenomenon is tumefaction, due to nutritive and vascular modifications which attend and explain the pyogenesis.

Pain, which is often the first appreciable phenomenon, is due to increased sensitiveness of the parts by the excessive influx of blood; to irritation or rupture of nerve filaments, and, finally, to compression of neighboring parts.

Heat and redness are two symptoms which have been described according to the evolution of superficial suppurations and which are attributed to an exaggerated afflux of blood, augmentation of nutritive exchange, and proliferation of cells. No experiments, however, have as yet been made to verify whether suppuration in deep-seated organs is also attended with a local rise of temperature.

When undisturbed, an abscess tends to open either into a neighboring organ or outwardly. When opened, whether naturally or surgically, the pus and the pyogenic microbes pass out of the focus, and this is followed by alleviation of the local and general symptoms. In some cases evacuation is accomplished at once, and cicatrization is soon established. More often, however, the pus re-forms and the process lasts for a more or less prolonged period.

The local manifestations are in most cases accompanied by general phenomena. When the latter appear in the beginning of the process, a grave infection is to be feared, since they indicate a special virulence of the pathogenic agent.

We do not need to dwell here upon the various disturbances which may be observed. They are those common to all infectious processes. The onset is characterized by chills; a rise of temperature then occurs; the fever may be continuous or remittent, or even frankly intermittent. At a more advanced stage it may assume a

hectic character, accompanied by secretory modifications, albuminuria, etc., which will be referred to again.

Cold Suppurations. From the point of view of their evolution, abscesses have been divided into two classes: hot abscesses, with an acute and clearly inflammatory evolution, and cold abscesses, characterized by a slow and indolent progress. The latter are often due to the tubercle bacillus. It was at one time assumed that they were always dependent upon the pathogenic agent named. Recent contributions demonstrate, however, that cold abscesses, whether cutaneous or osseous, are not necessarily of tuberculous nature. The author observed a case of cutaneous cold abscess due to a common pus coccus, the staphylococcus aureus.[1] Facts of this kind are not rare. Hallopeau[2] has reported two interesting cases, and Hulot,[3] in an interesting thesis, has described cutaneous suppurations which evolve like tubercular lesions and are attended by a progressive cachexia ending in death. These cold streptococcic abscesses are especially frequent in children, although they may also be observed in adults. A similar evolution may also be observed in cases of osteomyelitis.

In most instances, however, cold suppurations of the bones are due to Eberth's bacillus. We find in the memoire of Chantemesse and Widal a great number of observations proving the slow and insidious course of certain osteomyelites of typhoid origin.

Suppuration in the Various Parts of the Organism.

All parts of the organism are not equally liable to invasion by pyogenic microbes. Suppuration is rare in cartilages, owing, perhaps, to their scanty vascularization. There are, however, inexplicable differences between analogous tissues. Thus, while abscesses are quite frequent in the brain, the spinal cord is very seldom, if ever, the seat of a purulent focus. The same is true with reference to muscular tissue. There are but three muscles which are at times invaded by suppuration, namely, the iliac psoas, the sternocleidomastoid, and the deltoid. The resistance of the lungs is also very remarkable. In spite of the frequency of infections and the great number of pyogenic germs entering the respiratory tract, pulmonary

[1] Roger. Abcès froids dus au staphylocoque doré. Gazette hebdomadaire, August 6, 1892.

[2] Hallopeau. Abcès cutanés et sous-cutanés multiples et récidivants chez les jeunes enfants. Annales de dermatologie, 1894.

[3] Hulot. Infection d'origine cutanée chez les enfants. Thèse de Paris, 1895.

suppurations are quite limited and special. No more than small purulent points are observed in bronchopneumonic foci; the process is suppuration in the cavities. True pulmonary abscess is of very rare occurrence.

Whatever the suppurating organ or tissue under observation may be, the same pyogenic agents are always discovered. Aside from the specific suppurations, the microbes found in pus are generally the staphylococcus or the streptococcus, the colon bacillus, the pneumococcus, and less frequently the tetragenus or various species of minor importance. It is to be remembered, however, that the relative frequency with which these pyogenic species are met with varies considerably according to the part affected. It is readily conceived that the bacteriological nature of a suppuration must be related to the species normally inhabiting the region invaded.

Cutaneous Suppurations. The researches of Remlinger show that there are 40,215 bacteria to the square centimetre of skin. Forty-eight out of fifty colonies are composed of staphylococci. Consequently, when a suppuration occurs in the skin, this microbe will be found in most cases.

Buccopharyngeal Suppurations. It is not the staphylococcus but the streptococcus that is most frequently met with in buccopharyngeal suppurations, since the latter microbe is constantly present in the mouth. Some other pyogenic species, such as the tetragenus, pneumococcus, staphylococcus, *proteus vulgaris*, and colon bacillus are also found, but in small numbers. It is the streptococcus which easily becomes exalted and gives rise to the different varieties of phlegmonous sore throat and abscesses of the tonsils.

Nasal Suppurations. It is admitted that the staphylococcus is the microbe concerned in most cases of purulent rhinitis. There is no doubt that this coccus does produce nasal suppurations. The author has found it in abscesses of the septum in a state of purity. It is well to remark that the mucopus flowing from the nares before the abscess was opened contained no microbes other than the staphylococcus.

It is important to call attention to the frequency and gravity of purulent coryza of streptococcic origin in scarlatina.[1] It is an early manifestation characterized by a continuous discharge and often accompanied with enormous cervical adenopathies and suppurative

[1] Chausserie-Laprée. De la rhinite purulente dans la scarlatine Thèse de Paris, 1900.

otitis. The microscopic examination reveals the streptococcus almost in a state of purity. The streptococcus was found associated with the staphylococcus aureus in one case. This impure culture inoculated into a guinea-pig caused death of this animal in forty-eight hours.

Auricular and Ocular Suppurations. Otitis media may be due to anaërobic microbes, but in most cases it depends upon the streptococcus, pneumococcus, staphylococcus, tetragenus, the bacillus of Friedlaender, and the bacillus proteus. The pneumococcus is particularly frequent in primary otites, the streptococcus in secondary. All may give rise to lesions in more or less distant parts, especially to suppuration of the mastoid cells, phlebitis of the sinuses, abscess of the cerebrum and cerebellum, meningites, and even pyemia. When, however, suppuration has lasted for some time, the microbe or microbes which may have been present in the beginning of the process disappear and the staphylococcus alone is found. Such at least is the fact in odorless suppurations, since pus which becomes fetid contains anaërobic organisms capable of invading the mastoid and giving rise to gangrenous septicemia and to suppurative foci in distant parts.

Unlike the suppurations of the parts already mentioned, those of the eye seem to be due, in most cases, to specific microbes. Purulent conjunctivitis generally depends upon the gonococcus. Other microbes, however, may likewise be concerned, such as the bacillus of Koch-Weeks and the ordinary pyogenics.

Suppurations of the Respiratory Passages. In the deep parts of the respiratory passages the ordinary pyogenic microbe is the pneumococcus, as, for instance, in cases of bronchopneumonia, in which the streptococcus, the pneumobacillus, and the staphylococcus may also be found, but less frequently.

In cases of fibrinous pneumonia suppuration is exceptional. When it occurs it is due to a secondary infection with the staphylococcus aureus, seldom with the streptococcus or pneumobacillus. Contrary to classical opinion, however, it seems to be established that the suppuration of a pneumonic focus may be due to the pneumococcus alone. This is clearly evidenced by the observations of Zenker and especially by the researches of Griffon, who studied five cases of suppurative pneumonia.

Suppurations of the Digestive Canal. The colon bacillus and the intestinal streptococcus were until recently held to be chiefly respon-

sible for suppurations of the alimentary canal. The anaërobic species, and notably *B. ramosus* of Veillon, are at present supposed to play a more important rôle. Concerning this subject we possess very few documents. All we know with regard to phlegmonous enteritis is contained in the work of Ziegler and Mintz, who detected the streptococcus. The production of hemorrhoidal phlebites and anal abscesses is attributed to the colon bacillus. We are better informed as regards appendicitis. Most authorities admit the action of the colon bacillus and streptococcus. Veillon argues that the principal rôle is played by the *B. ramosus*, and he thinks that the fetid character of the pus and the gangrenous state of the walls prove the anaërobic nature of the process. Appendicitis is, therefore, held by many to be a variety of enteritis, its particular character being due simply to the special anatomical conditions of the affected part.

Experimental Appendicitis. In order to elucidate the mechanism of appendicitis experimentation was resorted to by Roux (of Lausanne). As, however, he operated upon the pig—an animal without an appendix—he previously created an appendix at the expense of the cecum, and obtained negative results. Taking up the question with Dr. Josué,[1] we operated upon the rabbit. The appendix of this animal differs from that in man in that it is far more voluminous and is in free communication with the cecum, but its analogy with the appendix of man is admitted by anatomists, such as Krause, Ribbert, etc.

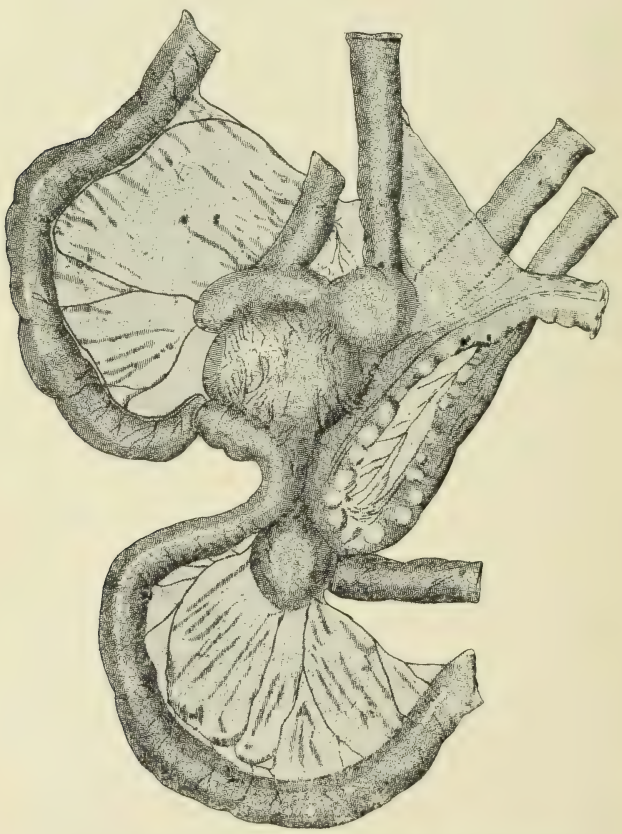
Some time after the publication of our researches on experimental appendicitis the question was taken up by Dr. Gervais, who confirmed our conclusions, and by Beaussenat, who obtained appendicites by exciting gastrointestinal disturbances. Dr. Chastanet[2] pursued experimental researches in our laboratory and demonstrated that it is possible to induce appendicitis in the rabbit by causing this animal to swallow microbic cultures. The appendix becomes affected the same as the other portions of the digestive canal, but its reparation seems to be less easy. Chastanet further determined this difference by producing traumatism in the various portions of the intestine and noticing that the lesions of the appendix persisted long after cicatrization of the lesions in the other parts. The lesions found in all these experiments were ulcers. These facts lead to the

[1] Roger et Josué. Appendicite expérimentale. Société méd. des hôpitaux, Jan. 31, 1896. Recherches expérimentales sur l'appendicite. Revue de médecine, June, 1896.

[2] Chastanet. Recherches expérimentales sur l'appendicite. Thèse de Paris, 1897.

conclusion that the appendix represents a lymphoid organ, comparable to the tonsil. Like the latter, it is frequently the seat of acute primary or secondary infections. This is what happens when the intestinal germs become exalted in consequence of some dietetic error, a depressing cause, or an infectious or other disease. The appendicular inflammation may be slight and be completely repaired. In other cases it is expressed by ulcerations, which are less easily

FIG. 2.



Experimental appendicitis of eighteen days' standing.

reparable. The latter may cicatrize or, on the contrary, give rise to adhesions which constrict the cavity and often obliterate it. Primary obliteration of the appendix is hardly conceivable. The idea that its obliteration represents the last stage of an ulcerating process seems to be in perfect harmony with the ensemble of published facts.

In our own experiments it was found necessary to inject virulent microbes into the intestinal cavity in order to induce appendicitis.

Aseptic ligation of the appendix is sufficient. The rabbits thus operated upon first lose flesh and seem to be suffering. They soon recover, however, grow fat, and no longer present any disturbance. Nevertheless, at the end of a few days, palpation of the abdomen reveals the presence of a deep-seated tumor, of greater or less size and consistency, situated to the right side of the median line. The majority of the animals thus survive almost indefinitely. They had to be killed in order to study the course of the lesions. Some rabbits died a few days after the operation. These suffered from a profuse diarrhea, and rapidly emaciated.

FIG. 3.



Experimental appendicitis of three months' standing.

The lesions vary, of course, according to the length of time since the operation. The day following the operation the walls of the appendix are found to be more vascularized than normally; its cavity is distended by a variable quantity of serosity. The second day the surface of the cavity is covered with a purulent layer. From the fourth, at times even from the third day onward, soft but highly vascularized adhesions are formed. The color of the appendix is milk-white, suggestive of a purulent transformation. The cavity contains a greenish substance. On the sixth day the appendix still presents an almost normal aspect, but it is closely adherent to the surrounding intestinal coils. Its contents are mixed with pus and some purulent floating flocculi.

The entire inside of the appendix then undergoes a purulent transformation. Coincidently, the walls become distended, so that toward the eighth day an ovoid cyst is found measuring about 3 cm. in diameter. (Fig. 2.) After having reached this degree of development, the purulent pouch seems to remain stationary, as we were able to convince ourselves by killing one of the animals three months after ligation of the appendix. (Fig. 3.)

In no case did we observe the pouch open into the peritoneum, but in several it was so thin at certain points that rupture might well occur sooner or later.

The microscopic examination of the pus reveals the presence of leucocytes and microbes. In old cases, the leucocytes undergo granulofatty degeneration. Bacilli are rare. In some cases it is

necessary to resort to cultures to demonstrate the presence of the colon bacillus.

Histological examination reveals extensive lesions. Fig. 4 represents the state of the walls three days after the operation. When slightly magnified, it is seen that the general structure of the appendix is preserved.

FIG. 4.



Wall of the appendix at the third day after ligation. × 8 diameters.

If a more advanced case is examined, for instance, one fifteen days old, it is seen that the normal structure of the organ has completely disappeared. (Fig. 5.) When slightly magnified it appears like a compact tissue with irregular contour, presenting here and there foci of necrosis.

FIG. 5.



Wall of the appendix fifteen days after ligation. × 6 diameters.

With high magnification is seen a fibrillary tissue with numerous nuclei. At certain points there are some foci of necrosis vaguely recalling the form of follicles. Elsewhere are found embryonic masses made up of infectious nodules. The presence of a few muscular cells may yet be perceived. It is impossible to detect microbes in the sections.

The importance recently attributed to foreign bodies in the appendix led us to make another series of experiments. We introduced into the appendix of two rabbits a ball of wax, of sufficient size in one of the cases to distend the intestinal walls. No disturbance resulted from the operation. The animals were killed at the end of a fortnight and no lesions were found. The appendix was absolutely normal. Moreover, the foreign body could not be found, as, in spite of its considerable size, it had been forced out by the contractions of the appendix.

From our series of experiments it is seen that only one experimental procedure produces ulcerative appendicitis, viz., complete ligation of the appendix. The cul-de-sac must be transformed into a closed cavity. Even double stricture does not cause inflammation, nor does the introduction of a ball of wax.

It now remains to account for the manner in which the suppuration of the appendix is produced when completely ligated. It is not the result of an arrest of the circulation, since the numerous vessels passing through the peritoneal fold amply suffice to insure the circulation. In fact, if, after having ligated the appendix, an appendicular fistula be created, by which the free extremity of the organ is connected with the exterior, no notable incident occurs. As soon, however, as the fistula is obliterated and the cul-de-sac is transformed into a closed cavity, suppuration sets in. This simple experiment demonstrates that suppuration is produced because an arrest of the flow of fluids occurs. We resorted to another series of experiments which proved that the suppuration is not due, as some authorities suppose, to exaltation of pyogenic germs. Cultures made with a few drops of the contents of a normal appendix proved capable of producing suppurative lesions in rabbits and death in nine days, while similar cultures prepared two or three days after ligation of the appendix had exactly the same virulence as those made before the operation. After the fourth day the pathogenic power of the intestinal contents declined rapidly. It is a general law, that in purulent foci microbes become progressively weaker, and even finally disappear. The mechanism of appendicular suppuration is the same as that governing the formation of all purulent foci. In fact, it is known that pyogenic microbes act by virtue of the soluble substances which they secrete. Under normal conditions, however, the products of the microbes in the appendix are discharged with the fecal matters. After ligation the toxins accumulate and, as the

experiments of Poliakoff have shown, the products of the pyogenic germs act particularly when they are elaborated slowly and progressively. We are thus led to the conclusion that appendicitis depends upon the general causes of suppuration. It is a tox-infectious lesion.

Abscesses of the Liver. The portal vein represents the main channel for the introduction of microbes into the liver. As hepatic abscesses are connected with intestinal lesions, it is the portal vein which, owing to its anatomical connections, insures morbid sympathy between the alimentary canal and the liver. In some cases germs pass through this vessel without leaving any trace, as is notably the case in dysentery. In other instances a suppurative pylephlebitis affecting the entire portal system and its contributory branches occurs and represents an intermediate incident accounting for the propagation.

After dysentery, we must also cite, among intestinal affections which give rise to hepatic suppurations, all those which are responsible for intestinal ulcerations: typhoid fever, tuberculous enteritis, typhlitis, and appendicitis. It is to be noted, however, that abscesses are as rare under these conditions as they are frequent in dysentery.

The most varied pyogenic microbes may be encountered in hepatic suppurations. The streptococcus as well as the colon bacillus and the staphylococcus are found. Dr. Lannois has reported an interesting observation of an hepatic abscess with Eberth's bacillus occurring in the course of a typhoid fever and caused by a pylephlebitis.

A point of interest in the history of hepatic abscesses is the fact that the pus is often sterile. This has been clearly ascertained in forty observations. As has already been remarked, every old suppurative focus finally becomes sterile, but some hepatic abscesses, by no means old, have been found equally free from microbes. The explanation is found in the well-known destructive action of the liver upon bacteria.

Dysenteric abscesses of the liver are seldom sterile. Out of thirteen cultures made by Kartulis, microbes developed in five instances. The staphylococci aureus and albus, and the *B. proteus vulgaris* were the species found under these conditions. On the other hand, examination of sections demonstrated that the walls of the abscesses contained bacteria, even when the cultures were negative. Such was the result in ten cases. There remain, therefore, but three observations of sterile abscesses.

Whether bacteria are detected or not, Kartulis always found amebæ. Some experiments pursued by Marchoux upon cats show that dysenteric abscesses of the liver may result from the injection of dysenteric stools containing amebæ.

Suppurations of the Pancreas. Although placed anatomically in a sufficiently analogous situation, the pancreas is far less frequently affected than the liver. Like the latter organ, it is infected either by germs carried to it by the bloodvessels or by bacteria entering it by way of the excretory channels. The conditions favoring infection are evidently the same in both instances. Pancreatic suppurations may, then, be observed in purulent infections, in variola, appendicitis and in consequence of lesion of the stomach and duodenum. The colon bacillus is the microbe found in the majority of cases, and it seems that the localization of this microbe is favored by the previous lesions of the organs—cysts, sclerosis, lithiasis.

Suppurations of the Urinary and Genital Organs. Like the digestive apparatus, the genito-urinary tract communicates by its terminal end with the external world. It may, therefore, be infected from without as well as from within. In man, however, protection against the outward germs is fairly well insured. Under normal conditions, microbes do not penetrate beyond the fossa navicularis. Nevertheless, bacteria are not infrequently found in the urethra of men otherwise healthy, notably the *streptococcus giganteus urethræ*. The bladder offers great resistance to microbic invasion. It is quite difficult to infect it when healthy. This is no longer true, however, when it is the seat of a lesion or when some obstacle opposes the free discharge of the urine. Upon a soil thus prepared the most varied pathogenic agents develop abundantly, inducing suppuration of the bladder, ureters, pelvis, and kidneys. They may even go farther and give rise to perinephritic phlegmons.

The gonococcus, which is to-day held to possess greater migratory powers than was formerly believed, represents in women an important cause of salpingitis. According to the researches of E. Reymond, it vegetates upon the surface of the mucous membrane in the desquamated epithelial cells and but exceptionally invades the walls of the Fallopian tubes. In streptococcic salpingitis, on the contrary, the microbe strongly tends to propagate toward the peritoneum. Finally, the salpingites due to the colon bacillus are observed in those cases in which adhesions are formed between the intestine and the Fallo-

pian tubes. This fact leads to the opinion that the colon bacillus is derived from the intestine.

Suppurations of the Nerve Centres. The other parts of the organism not communicating with the exterior cannot be attacked by pyogenic microbes, except as a result of traumatism, which allows them to penetrate directly, or of extension of a neighboring lesion, or of a general infection ending in localizations. The relative frequency of the microbic species found under these conditions will at times depend upon the situation of the part affected. Abscesses of the cerebrum and cerebellum being in most cases consecutive to otitis, the microbes found are those concerned in suppurations of the middle ear.

Suppurations of the Serous Membranes. Serous membranes are generally invaded by contiguity, as a result of a purulent focus developing in subjacent organs. Such, however, is not always the case. Localization may first occur in the nervous system, as is the case with articulations. The same is true with regard to the meninges, pleura, and peritoneum.

In the pleurisy of children the pneumococcus is the microbe commonly found. The streptococcus is comparatively seldom met with. In adults, on the contrary, the streptococcus is more frequently found than the pneumococcus. Among the other pyogenic microbes, we may cite the staphylococcus, the bacillus of Friedlaender, the typhoid bacillus, and the colon bacillus. These findings are not merely of theoretical interest. It is known that recovery from purulent pleurisy is very frequent in cases in which the pneumococcus is the pathogenic agent. The differential diagnosis may be at least suspected, if not established, by simply taking into account the course of events and especially the characters of the fluid. In the majority of cases the pus of pneumococcic pleurisies is thick, viscous, and greenish. That of streptococcic pleurisies contains a greater proportion of serum and gives a grayish deposit. Certainty is, of course, to be reached only by bacteriological research. In this connection it may be stated that a purulent pleurisy, the fluid of which is free from bacteria, must be considered tuberculous in nature (Fraenkel).

The principal cause of peritonitis being in the intestines, it is readily conceived that peritonitis due to the colon bacillus must be quite frequent. The intervention of the colon bacillus also accounts for typhoidal peritonites. This is not invariably the case, however.

Fraenkel has reported a case in which the exudate of a peritonitis occurring in the course of a typhoid fever contained no other microbes than the typhoid bacillus. When infection of the peritoneum occurs through the genital organs, as is the case especially in women, the gonococcus is sometimes found, but more frequently the streptococcus.

In most cases of purulent pericarditis the inflammation depends upon a general infection, but it may occur independently or accompany other purulent lesions affecting the viscera or serous membranes. That is to say, purulent pericarditis is seldom primary. It represents the localization of an infection the starting point of which escaped observation. Suppurative pericarditis sometimes occurs as a result of affection of the respiratory apparatus—*i. e.*, pneumonia, bronchopneumonia, even dilatation of the bronchi, and, in these instances, it is due to the pneumococcus. It is sometimes consecutive to an eruptive fever: measles, varicella, and, above all, scarlatina and smallpox. It is, however, a complication of far rarer occurrence than was formerly believed. My own statistics, including 5334 cases of eruptive fevers, show but two cases of purulent pericarditis.

The pneumococcus and streptococcus are the two microbes most frequently concerned in purulent meningitis. Among the bacteria of uncommon occurrence we may cite the staphylococcus aureus, the typhoid and colon bacilli, and the bacillus of influenza. We do not include the meningites of specific nature, caused by Koch's bacillus, and the epidemic cerebrospinal meningitis which depends upon a particular microbe—the meningococcus of Weichselbaum (diplococcus intracellularis), formerly confounded with the pneumococcus.

Meningitis is not frequent in eruptive fevers. I have met with but one case. An otitis, developing in a man convalescing from measles, became the starting point of a purulent infection. Numerous suppurative foci appeared in the joints, and at the necropsy the meninges were found full of pus. This lesion, in spite of its intensity, had remained absolutely latent. The patient had retained consciousness to the last, and never complained of any suffering in the head. The absence of morbid manifestations is probably to be attributed to the absence of dropsy of the ventricles. The author would like to remark that, at all events, suppurative meningites, even when extensive, occur in a latent manner oftener than is believed. They are expressed by no symptoms whatever.

If we consider the ensemble of the results to which the study of

suppuration leads us, we perceive that pus originates when the leucocytes fail in their task of destruction of the invading microbes. Numbers of cells are killed by microbic secretions. Their cadavers constitute the pyocytes—useless cells, true foreign bodies—which must be eliminated. If these are not very numerous, the macrophages remove them. In most cases, discharge occurs outwardly and suppuration becomes established. Suppuration, then, is the establishment of an exit for the microbes, toxins, and destroyed cells.

Suppuration is a common process to which a great number of parasites may give rise. But all of them act in the same way, viz., by secreting necrotizing substances. Suppuration is reaction against toxins. In order for this reaction to be produced, the organism must possess a certain degree of resisting power. If it is incapable of reacting, two events are possible: first, reaction being insufficient or *nil*, the pyogenic micro-organisms invade the whole organism; they cease to produce pus, and give rise to septicemia. Second, the necrotizing action of the toxins is so strong that the tissue cells undergo fermentations analogous to those which characterize putrefaction. We then find ourselves confronted by a new process—another termination of inflammation—related to suppuration by numerous transitions. It is this process that we are now about to study, namely, gangrene.

CHAPTER VIII.

GANGRENE.

Definition of Gangrene. Causes Favoring the Development of Gangrene. Importance of Vascular and Nervous Lesions. Auxiliary Rôle of Certain Toxic Substances. Study of the Principal Agents of Gangrene. Rôle of Anaërobic Microbes. Rôle of Facultative Anaërobics. The Agents of Gangrenous Mammitis. The Microbe of Benign Gangrene of the Eyelids. Rôle of Pyogenic Microbes. Relationship between Suppuration and Gangrene. Gangrene in Different Parts of the Organism. Chemical Analysis of Gangrenous Products.

Gangrene is a morbid process essentially characterized by the mortification and putrefaction of tissues.

There can never be putrefaction without microbes. Gangrene, then, is always of microbic origin, and should be distinguished from aseptic mortifications which are designated as necrobioses. The distinction is not, however, as sharp as may appear at first sight. There are microbic gangrenes in which mortification is the predominant phenomenon, attended by little, if any, putrefaction. These are cases of dry gangrene closely related to simple necrobioses. In a great number of cases experimental and bacteriological investigations have not been sufficiently complete to determine whether the process is due to an infection or merely to cellular disturbance. In cases of toxic gangrene, like ergotism, or trophic gangrene, like ulcerating dermosynovitis, it is not known whether the process is due simply to poisons or nervous lesions or to a superadded infection occurring in tissues no longer capable of resisting microbic invasions. The latter view seems to me more rational, but it is not accepted by all, and must be held subject to modification.

Gangrenes, properly so called—*i. e.*, those of microbic origin—cannot develop except in parts which are in direct or indirect communication with the exterior. They are observed in the skin, mucous membranes, and the respiratory apparatus. Tissues or organs not in contact with the air (abdominal viscera, nerve centres) cannot be the seat of gangrene unless a primary focus, whence microbes may penetrate the organism, exists. Suppose, for instance, that the artery of a limb is obliterated, gangrene may appear in the parts deprived of circulation. Such is the case in senile gangrene.

If, however, the obstruction occurs in a cerebral artery, necrobiosis or softening, but no gangrene, results.

There is no specific microbe of gangrene. The process is a commonplace one, and what we said with regard to suppuration can also be applied to it. As in that case, pathogenic agents may be divided into two groups. Some of them, when in contact with healthy tissues, possess the power to engender the two stages of gangrene—the mortification of living elements and their putrefaction. Others act only upon altered, partly mortified tissues. In the latter instance pyogenic microbes are found in the morbid focus, and they act upon the diseased organism as they do upon lifeless matter. No doubt, the division is not absolute. The development of even the most virulent microbes is materially facilitated by a great number of accessory causes, such as mortification and chemical alterations of tissues and the association of different microbes. These conditions are not indispensable, however, and occupy a secondary place. Their intervention is of prime importance when the invading microorganisms are of the kind which become capable of giving rise to gangrene only on favorable occasions.

Among the latter are the pyogenic microbes. This is not surprising, since we have shown that in all suppurations two successive acts are to be distinguished: namely, the necrosis of the invaded tissue and the reaction of the organism, resulting in the production of cells which make up the purulent exudate. For the production of the second phenomenon a certain degree of reactionary power is required. If the tissue is altered or the organism profoundly debilitated, the necrotic process prevails, and gangrene develops. In nearly all instances, however, the organism makes some reactionary effort to eliminate the dead elements, and suppuration appears secondarily around the slough. This result is observed, even when the process is due to the specific agents of gangrene, provided they are attenuated. The septic vibrio, which is the type of this kind of microbes, produces gangrene when very active or when inoculated into susceptible animals, but recedes to the rank of a pyogenic when it is attenuated or when the animals possess a higher degree of resistance. In brief, the pyogenic microbes when exalted become necrogenic; the necrogenic microbes when attenuated become pyogenic.

As we have already noted, two stages are observed in gangrene: namely, necrosis and putrefaction. This has led some authorities to

compare or even identify gangrene with the process of putrefaction occurring in the cadaver. The analogy should not be overemphasized. A dead tissue abandoned to putrefaction does not present the same aspect as a gangrenous part, and yet the microbes developed may be identical in both cases, and chemical analysis may reveal similar transformations in both tissues. The difference lies in the fact that, in the production of gangrene, a part is played by the living element—*i. e.*, the reactionary process. No one, however, has as yet attempted to demonstrate the differences. All we can do, therefore, is to offer a few reflections intended to show how, in our opinion, the experiments should be pursued in this connection.

One difference between putrefaction and gangrene must depend upon arrest or persistence of the circulation, viz., influx of blood serum, lymph, leucocytes, and coloring matters of the blood. The latter, by being decomposed, must contribute to the color of gangrenous tissue. These various conditions, however, do not suffice to explain all phenomena: Firstly, because the circulation is at times interrupted, as in the case of dry gangrene, and yet the process retains its special character. Secondly, when we cause putrefaction in a tissue immersed in blood we render the process more intense, but we do not produce gangrene. We are thus led to the conclusion that gangrene is dependent upon the action of putrefactive process upon living cells—*i. e.*, upon cells capable of responsive action—and that the peculiar appearance of the gangrenous parts is due solely to this cellular reaction. In other words, cadaveric putrefaction is characterized by the development of saprophytes which act upon dead matter, viz., matter incapable of reaction. On the other hand, gangrene is characterized by the development of microbes which attack healthy, sometimes profoundly altered cells, but cells which have not passed into a state of vital indifference. Our definition must, therefore, be somewhat modified, and, in order to sharply distinguish gangrene from cadaveric putrefaction, we may state that *gangrene is essentially characterized by putrefaction of healthy or diseased but still living cells.*

Causes Favoring the Development of Gangrene.

Even when gangrene seems to be primary it develops only in deep wounds which contain, in addition to the principal agent, a multitude of pyogenic or saprogenic bacteria without the assistance of which the process would not have occurred.

In other cases gangrene appears as a secondary manifestation either in the course of an infection or in a subject suffering from some non-microbic disease. It generally develops in organisms debilitated by cachexia, fatigue, or starvation.

Gangrene at times first occurs at a point of the economy which was spared by the initial affection. When it develops in a locality that is already the seat of a previous lesion it represents a local epiphenomenon superadded to the pre-existing alteration. This is observed in variola, varicella, even vaccinia, as well as in various cutaneous affections, such as purpura, erythema nodosum, and pemphigus. This is what is also observed in mucous membranes and in the viscera. A great number of necrotic laryngites and enterites and various forms of pulmonary gangrene belong in this group. The gangrenous process sets in and is assisted by a previous lesion.

When gangrene appears as a primary lesion its development is facilitated by all causes which profoundly disturb the nutrition of tissues, either directly (contusions, action of physical or chemical agents) or indirectly. In the latter instance the influences favoring the development of gangrene arise from vascular, nervous, or humoral alterations—compression and obliteration of vessels, arterites, and edemas. Symmetrical gangrene of the extremities is a good illustration of the rôle of nervous alterations.

The following is a classification of the pathogenic conditions of gangrene which, although artificial, is fairly applicable to the majority of cases:

CONDITIONS PREDISPOSING TO GANGRENE.

Indirect alteration of tissues by . . .	Mechanical agents.	
	Physical agents.	
	Chemical agents.	
	Animate agents.	
Direct alteration of tissues by . . .	Circulatory disturbances .	Edemas.
		Vascular compression and obliteration.
		Arteritis.
		Arteriosclerosis.
	Nervous disturbances .	Central alterations.
		Neuritis.
		Raynaud's disease.
	Dystrophic disturbances .	Humoral and diathetic affections (Bright's disease, diabetes, etc.).
		Autointoxications.
		Exogenic intoxications.
		Infections.

It is well to remark, however, that in reality the events are more complex and that in a given case several pathogenic factors usually intervene. Let us take, for example, the phenomena occurring in cases of infection. The predisposing cause of the gangrene is represented by intoxication of the organism due to the secretions of

pathogenic microbes, by alterations occurring secondarily in the viscera and by disturbances of cellular metabolism. As a rule, however, intoxication alone is not sufficient. Account must be taken of the local lesions secondarily caused by microbes in the skin or viscera—in the lung, for instance—as well as of alterations manifested in the arteries, capillaries, and nerves. Moreover, we must not overlook the fact that fever diminishes the secretions, notably those of the mouth, and that if the patient is not properly taken care of the fecal matters and the urine soil the orifices and create foci of putrefaction which deal the last blow to the failing resistance of the organism. Hence, with the progress of hygiene and antisepsis, secondary gangrenes are of far less frequent occurrence.

What has been stated with reference to infections may be repeated in regard to each of the pathogenic processes above admitted. In every instance the mechanism is complex. We shall endeavor to briefly study each predisposing cause independently.

Role of Mechanical and Physical Agents. The importance of traumatic mortifications caused by mechanical agents has been demonstrated by numerous contributions of great interest. In this connection, Dr. Arloing's remarkable study of his *bacillus heminecrobiophilus* is worthy of consideration. This microbe is incapable of producing gangrenous putrefaction in healthy tissues, but easily invades tissues altered by traumatism. The same is true as regards the other agents of gangrene. Even the bacillus of gaseous gangrene, if freed from toxin and introduced in small amount, gives rise to no lesion. Lesions are produced, however, when it is deposited in a muscle that has been subjected to violent contusion.

Analogous results occur when physical agents are permitted to act upon tissues. Intense cold or excessive heat produces a series of cellular mortifications. Small aseptic eschars may result, and in connection with these the germs of gangrene may develop and give rise to characteristic alterations in the tissues, as a consequence of necrotic lesions or the formation of phlyctenulæ.

Physical agents, however, do not always act at the point of application. A considerable number of observations tend to demonstrate that exposure to sudden and intense cold may induce pulmonary gangrene. In this instance the action of cold is probably indirect. It is characterized by a spasm of the pulmonary vessels which, causing anemia in the tissues, renders them more vulnerable, and thus favors the development of necrosing agents.

Role of Chemical Agents. As is known, chemical agents are divided into caustics and toxics.

Caustics diminish the resistance of the tissues and may even produce necrosis liable to gangrenous putrefaction. This result, however, is rarely realized, and the action of caustics from the point of view now occupying us is far less important than that of toxics.

Those toxic substances which produce gangrene at the point of their introduction are very much like caustics. Venoms belong to this group. The bites of snakes, of certain fish, the sting of insects and scorpions may be followed by gangrenous phlegmons. Careful researches, however, tend to demonstrate that the necrosis is due rather to the microbes contained in the venom than to the venom itself. The venom is to be credited only with the production of cellular disturbances which facilitate the development of the microbic agents. The situation is the same as the one resulting from the infiltrations of bile or urine, except that the action of the venom is more intense. In fact, the bile, when injected beneath the skin of a delicate region—for instance, the ear of a rabbit—produces a necrosis ending in the loss of a part of the organ.

The urine seems to be less harmful. Its action is due chiefly to the distention of the tissues injected, which become thereby good culture media for microbes. The conditions are the same as in the experiment of Prof. Bouchard, who injected non-sterilized alimentary substances beneath the skin of rabbits. The animals rapidly died with gangrenous lesions infiltrated with gases. The subcutaneous fluid swarmed with bacteria, but inoculation of the latter into healthy animals produced no disturbances—the parasites were incapable of overcoming the resistance of a normal tissue.

Role of Circulatory Disorders. Any cause that diminishes the nutrition of cells predisposes to gangrene. Samuel, experimenting upon rabbits, produced anemia in the ear by ligating the carotid and posterior auricular arteries. He then produced an intense inflammation in both ears either by immersing them in hot water or by rubbing them with croton oil. The healthy side rapidly returned to a normal state, the anemic side became the seat of gangrene. The writer has noticed that the results are the same when inflammation is induced by means of the staphylococcus. Under these circumstances the anemic part presents lesions with gangrenous tendencies. Similar facts are often noted in clinical observation. Senile gangrene, which invades a limb in which the artery is obliterated, and

sphacelus consecutive to acute arteritis, are well-known illustrations. Venous obliterations may likewise favor the development of gangrene, but less frequently, since circulation is easily re-established by collaterals.

Edemas, no matter how caused, similarly dispose the parts to gangrene by distending the tissues and thus disturbing nutritive exchanges.

Role of the Nervous System. The influence of the nervous system in the pathogenesis of gangrene is beyond question. It will suffice to recall the eschars which at times appear so rapidly in consequence of some cerebral or spinal lesion and the cases of extensive gangrene following neurites, reported by Pitres and Vaillard. We may add Raynaud's disease. The vascular disorders characterizing this affection explain the pathogenesis of those small eschars appearing especially in the fingers and toes—*i. e.*, at points where multitudes of saprophytes swarm, some of which may acquire pathogenic power. The influence of nervous disturbances upon the development of gangrene is also evidenced by the experiments pursued by us with the streptococcus of erysipelas. Section of sensory nerves augments the intensity and duration of the lesions and favors the development of gangrenous patches.

Role of Intoxications. The diseases that disturb the chemical constitution of the organism, especially those inducing autointoxication, induce gangrene by a highly complex mechanism, for, when they last for a certain length of time they give rise to visceral lesions and arterial and nervous alterations which contribute to the development of sphacelus. Thus, in Bright's disease it is almost impossible to determine the respective parts played by the various lesions and by the blood alterations. The difficulty is equally as great in diabetes. The arterial lesions, the nervous alterations, and the dyscrasic modifications are alike responsible for the gangrenous process. We have already recalled, in connection with suppuration, the experiments of Bujwid and of Nicolas which demonstrate that the staphylococcus aureus produces gangrene when it is inoculated into a rabbit rendered glycosuric by intravenous injection of grape-sugar.

The problem is still more complex when we consider exogenic intoxications. The rôle of arterial spasm has been admitted by some authorities to account for gangrenes produced by ergot. The experiments of Kobert have demonstrated that this action is due to a

special acid, sphacelic acid. Is it to be assumed that a spasm renders the part anemic, and thus enables the microbes to develop? This explication cannot be admitted without reserve, since the experiments of Holmes and of Wernich tend to demonstrate that ergot does not produce a tetanic state in the small arteries, for tension is lessened.

Principal Agents of Gangrene.

Bacteriology of Gaseous Gangrene. The type of microbes capable of giving rise to primary gangrene is represented by the *bacillus of gaseous gangrene*, also called *vibrion septique* (Pasteur), *bacillus of gangrenous septicemia*, *bacillus septicus gangrenæ* (Arloing), *bacillus of malignant edema*, *bacillus œdematis maligni* (Flügge).

As is known, the microbe in question is an anaërobic bacillus, generally occurring in the form of motile rods, measuring on an average 3μ in length and 1μ in breadth. It occurs singly or in groups of two or three, at times forming short chains. In cultures these bacilli are, as a rule, solitary and, at the end of a certain length of time, form undulating filaments sometimes assuming a spiral form. The filamentous forms are observed in animals, notably in the blood, where they reach a length of 20μ and even 40μ. They are easily stained, but are decolorized by Gram's method.

The bacillus of gaseous gangrene is strictly anaërobic and develops in various media, provided air is excluded from it. The cultures grow at 68 F. (20 C.), but are more luxuriant at 98.6 F. (37 C.). This bacillus is pathogenic for man, the horse, sheep, pig, and guinea-pig. The rabbit is a little more resistant. The dog is rather susceptible.

The symptoms produced in man have been described under the names malignant edema (Pirougoff, Koch), acute purulent edema (Pirougoff), swift gangrene (gangrène foudroyante, Maisonneuve, Salleron), invading traumatic gangrene (Bottini), gangrenous septicemia (Chauveau, Arloing).

The designation gaseous gangrene, proposed by Poncet, seems to us by far the most preferable. It has the advantage of expressing the two main manifestations of the morbid process.

Being anaërobic, this bacillus cannot vegetate in superficial wounds exposed to the air. It invades only deep, contused wounds contaminated with dust. It rapidly develops in mortified tissue, giving rise to patches of sphacelus and an exudation which exhales a fetid odor and is filled with corrupt gases. At times the lesion spreads with

extraordinary rapidity and causes death within a few days, with the appearance of general manifestations which clearly indicate the profound intoxication of the organism, and are expressed by rapid prostration, dyspnea, and, at the end, a fall of temperature.

Animals are liable to gaseous gangrene as well as man. A certain number of cases have been reported occurring in the horse, cow, and rabbit, after traumatism or parturition. Among laboratory animals the guinea-pig is the most sensitive.

The results of numerous experiments demonstrate that the bacillus of gaseous gangrene acts the same as the saprophytes of putrefaction. The value of the author's classification is thereby diminished, since this microbe is not of itself capable of overcoming the resistance of the organism, although it is true that the same remark holds good with regard to almost all pathogenic agents.

The Various Agents of Gaseous Gangrene. Along with the bacillus of gaseous gangrene are to be classed a series of microbes which are more or less similar to it in their biological or pathogenic characters.

One of them is the bacillus of symptomatic anthrax,[1] which has sometimes been considered a particular species, sometimes a variety of Pasteur's bacillus. It differs from it by its pathogenic properties. It attacks mostly cattle and sheep. The ass, horse, and white rat present only local symptoms. The dog, cat, pig, rabbit, chicken, pigeon, and duck are refractory, while the guinea-pig is as sensitive to it as it is to gaseous gangrene. No case of transmission of the disease to man has thus far been reported.

Natural immunity, however, is no more absolute in this than in other cases. The author[2] has demonstrated that it is possible to overcome the resistance of the rabbit to symptomatic anthrax by several procedures: namely, by simultaneous injection of a living or sterilized culture of the *B. prodigiosus*, of *proteus vulgaris*, or of *staphylococcus aureus*—by injection of soluble substances extracted from cultures of *B. prodigiosus* by means of glycerin and precipitated by alcohol—by intravenous injection of soluble products of symptomatic anthrax, and by inoculation of the virus into the anterior chamber of the eye. Finally, as in the case of septic vibrio, animals

[1] Arloing, Cornevin, and Thomas. Recherches expérimentales sur la maladie infectieuse appelée charbon symptomatique. Revue de médecine, 1880.

[2] Roger. Contribution a l'étude expérimentale du charbon symptomatique. Revue de médecine, March and June, 1891.

may easily be vaccinated against symptomatic anthrax by means of living or sterilized cultures. The animals thus rendered refractory furnish a germicidal and therapeutic serum.

Gaseous gangrene may also be produced by other microbes, such as the *pseudo-œdem bacillus* of Liborius (*B. pseudosepticus*, Macé), the *B. phlegmones emphysematosæ* (Fraenkel), or *B. perfringens* (Veillon and Zuber), which is an anaërobic; *B. œdematis aërobicus* of Klein, the *B. pseudo-œdematis malignæ* of San Felice, and the *aërobic septic bacillus* recently described by Legros and Lecène.

Necrosing Role of Pyogenic Microbes. Of the micro-organisms above described, several which produce gaseous gangrene in certain animals are simply pyogenic for more resistant species. Reciprocally, common pyogenic germs are capable, under certain circumstances, of creating gangrenous lesions.

The streptococcus is the leader of those pyogenic germs which occasionally become capable of giving rise to necrosis. This seems to be the microbe causing the experimental disease which Koch produced by inoculating putrid substances into the mouse and which he designated as progressive necrosis. We have repeatedly stated that erysipelas produced in the rabbit's ear by the streptococcus may terminate in sphacelation. On the other hand, injection of a culture of streptococcus into the peripheral end of the crural artery in a rabbit is at times followed by gangrene of the limb. We must add that, under these conditions, examination of the mortified parts shows numerous auxiliary microbes, but these occupy the most superficial parts and evidently play a rôle of secondary importance.

Analogous facts are observed in man. Intense erysipelas of the face often produces necrosis of the eyelids. The same is a possible event with regard to the testicles. Erysipelas may be followed by gangrene of the scrotum. In a case of complete sphacelation of the scrotum the skin was gradually detached and the testicles exposed. This was then followed by active granulation, and the lesion was completely repaired.

Another pus coccus, the staphylococcus aureus, may also produce gangrene. This, like the streptococcus, is a facultative anaërobic. The experiments of O. Bujwid establish that the staphylococcus engenders gangrene in animals rendered glycosuric. Other observations tend to show, though not conclusively, that this micro-organism may also produce gaseous gangrene. Lastly, there is the bacillus

proteus, the action of which is incontestable, since it is a pyogenic microbe endowed with a high degree of fermentative power.

Gangrene in Various Parts of the Organism.

Cutaneous Gangrene. The majority of cutaneous lesions may be complicated by gangrene. Not to mention anthrax and erysipelas, which have already been referred to, we should like to recall the possibility of gangrene in connection with the most varied and at times the slightest lesions, such as impetigo, variola, vaccinia, ecthyma, herpes, zona, purpura, and even urticaria. Sphacelation is favored by all debilitating causes, and often coincides with visceral lesions, diarrhea, and bronchopneumonia. In other instances gangrene of the sacrum is observed in the course of convalescence from a grave disease. A cerebral or spinal lesion is at times responsible for the gangrenous process. It is readily conceivable that, under these various conditions, the pus cocci and saprophytes—normal residents of the skin—may easily develop and, by their association, create gangrene.

Gangrene of the Limbs. Instead of remaining limited to the skin, gangrene may invade a more or less considerable part of a limb. This is notably observed in the course of acute arterites consecutive to infectious diseases. The lesion is due to the obliteration of the vessel by a microbe—the streptococcus in the majority of instances. The ischemia resulting therefrom leaves the tissues in a state of absolute impotence against the toxins secreted by the pathogenic agent and, incidentally, against the microbes tending to penetrate the skin.

An affection which we have endeavored to individualize under the name benign gangrene of the eyelids[1] is related to gangrenous lesions of the skin. The germ concerned in the lesion was a large micrococcus, staining by Gram's method, and developing preferably in aerated media.

Gangrene of the Mammary Glands. Although the word gangrene immediately suggests the idea of a grave process, we have already referred to cases in which the evolution is favorable and even benign, as is often the case with gangrene of the eyelids and genital organs. The same is true with regard to gangrenous mammitis.

Investigations in comparative pathology have shown the fre-

[1] Roger and Weil. Gangrène bénigne des paupières. Presse médicale, 1901.

quency of gangrenous mammitis in milk yielding females, notably among bovidæ. In a great number of cases the presence of streptococci of peculiar characters has been reported. Kitt, Lucet, and Guillebeau have described other pathogenic agents. No researches having been pursued as to the human species, reference must be made to a case which the author studied with Dr. Garnier.[1] A woman, aged seventeen years, had been confined on March 1, 1899. The child had died two days later, without any definite cause. On March 7th she complained of malaise and pain in the throat. On the 9th a typical scarlatinal eruption appeared upon her body and she was immediately sent to the isolation hospital of la Porte d'Aubervilliers.

From the time of her admission the state of her left mamma attracted our attention. The skin of the region presented a diffuse redness, especially marked toward the internal and lower part, where two patches of ulceration with sphacelated base were noted. There was abundant fetid discharge. Other smaller ulcers developed around the areola. The gland itself was swollen and very painful on palpation.

Moist dressings, constantly applied to the diseased region, in no way modifying the condition, the odor of the purulent discharge soon became plainly gangrenous; the lesion itself began to spread, and the ulcerations assumed a dark color. We then prescribed dressings with peroxide of hydrogen. Improvement was immediately manifest. A grayish eschar separated, eliminating the mortified glandular tissue. Three weeks after the beginning of the disease cicatrization was completed.

The pus taken from the wound was examined and cultured in various media. Several series of inoculations with the pus were made into rabbits and guinea-pigs, for which it proved pathogenic; less so, however, for the latter than the former. The predominating microbe was a small micrococcus whose clearly rounded elements were usually solitary, sometimes associated in couplets, and exceptionally forming groups of three. They were free among the cells, and none were found inside the leucocytes. In addition to this microbe, some chains of streptococci were observed, but they were comparatively few in number.

The results obtained by the several series of inoculations were sufficiently uniform to demonstrate that the microbe isolated by us

[1] Roger and Garnier. Note sur un cas de mammite gangreneuse. La presse médicale, July 22, 1899.

was a pathogenic agent, capable of giving rise to grave and extensive suppurative lesions. The development of the gangrenous mammitis may, it seems to us, be legitimately attributed to this microbe.

The micrococci found in the gangrenous mammites of milk-yielding females may be compared to the one isolated by us in the human subject, but the comparative study which we have pursued shows that our microbe preserves its own individuality. Its cultural characters and its pathogenic action upon laboratory animals do not permit its confusion with other species already described.

Gangrene of the Mouth and its Adnexæ. There is an affection of the mouth which may be looked upon as a superficial and benign gangrene. We refer to what is improperly designated as ulcerative membranous stomatitis. In reality, the so-called false membrane is nothing more than the mortified mucous membrane. Many authorities have studied this affection with the view of detecting a specific microbe, but with no encouraging results. Pasteur and Netter observed the presence of spirilla in the patches. Frühwald noticed the same elements associated with cocci, bacilli, and filaments of leptothrix. According to Gallipe, the probabilities are that there is no specific microbe and that the disease is created by buccal saprophytes which have become exalted by various causes—the evolution of a wisdom tooth, for instance. However, the researches of Vincent, by proving that chancriform tonsillitis is due to the combined action of the spirilla of the mouth and fusiform bacilli, give a certain value to the older researches of Netter.

The true gangrene of the mouth—noma—is one of the affections which has become rare, owing to the progress of antiseptic practice. As early as 1878 Sanson noticed in the blood the presence of microbes, but these were in nowise pathogenic. Jordan and Morse made similar observations. During an epidemic of measles raging in Munich, Ranke had the opportunity to study six cases of noma. Microscopic examination revealed numerous microbes, particularly diplococci and streptococci, but inoculation into the rabbit produced no result. By examining sections of tissues preserved in alcohol, Rossi found masses of rods, staphylococci, streptococci, and leptothrix. The results were analogous in a case studied by Babes, who encountered leptothrix, spirilla, the streptococcus pyogenes, the staphylococcus aureus, and an ovoid bacillus. In a more recent contribution Babes announced that he had isolated a very slender bacillus whose cultures injected into the cheek of a rabbit produced

a gangrene similar to noma. This highly interesting result is to be classed with that obtained by Schimmelbusch.[1] In the case reported by the latter authority there were found at the centre of the eschar a multitude of various microbes. At the periphery, however, there were none but slender bacilli, with rounded extremities, occurring singly or in couplets, and capable of growing into filaments. Inoculation of either the cultures or the mortified tissue into the rabbit produced only abscesses. In two chickens patches of necrosis developed and were healed in three weeks.

Gangrenous angina is not always connected with the diphtheritic process. It may be primary. Excluding the cases of superficial gangrene, however, which are related rather to the study of pseudo-membranous anginas, true gangrenous angina is a rarity. Out of a total of 701 observations, the author has collected but three cases.

Gangrene of the Respiratory Apparatus. Two varieties of gangrenous processes may be distinguished. One, comparatively benign and often curable, in which the superficial lesion remains limited to the bronchi; the other, profound, invading the parenchyma.

In cases of fetid bronchitis the most varied microbes have been found. Rosenstein met with the *oidium albicans;* Canalis, with actinomycetes; Leyden and Jaffé, with the leptothrix pulmonalis. Lancereau observed diplococci; Marfan, the *bacterium termo,* and Noica, the colon bacillus. One of the best studied observations is that of Lumnitzer. He found four staphylococci: the S. albus, citreus, cereus flavus, and cereus albus; one diplococcus, and one bacillus.[2]

Pulmonary gangrene has much oftener been the subject of bacteriological researches. As early as 1846 Virchow noticed in the gangrenous fluids the presence of sarcina resembling those found in the stomach. Fischer collected eighteen observations of this kind, four of which are his own.

The most recent contributions show that the most varied microbes may be encountered in the foci of pulmonary gangrene. Those most frequently found are the buccal spirillum, the *proteus vulgaris,* the streptococcus, the *staphylococcus aureus,* tetragenus, and the leptothrix. Moreover, various pathogenic bacteria may be met with

[1] Schimmelbusch. Ein Fall von Noma. Deutsche med. Wochenschrift, 1889, No. 26.

[2] Lumnitzer. Adatok a rothaszto hörglob koroktana és tünettanahoz (contribution to the etiology and symptomatology of putrid bronchitis). Orvosi Hetilap, 1888 (Anal. Central. f. Bakteriologie, 1888, Bd. iii. p. 621).

which vary from one case to another. Guillemot,[1] who has reported the results of his studies in thirteen cases of pulmonary gangrene, attributes an important rôle to anaërobic microbes in the production of the process, and regards them even indispensable. It is true, however, that these anaerobic agents are not highly virulent. They must be inoculated in large doses or associated with other species, notably to aërobics, in order to give rise to morbid phenomena.

In two of the author's cases, one observed in 1885 the other in 1895, the pulmonary gangrene seemed to have been produced by saprophytes developed in a primary focus created by the pneumococcus or streptococcus. In both cases, however, these cocci had rapidly lost their virulence and had done no more than prepare the soil for the development of putrefactive agents. However that may be, the pyogenic micro-organisms seem to play an important rôle. Issuing from a purulent focus, they have been known to be arrested in the lung and there form the starting point of a gangrenous lesion. Bonome, who had the opportunity to examine nine cases of pulmonary gangrene, found the streptococcus five times, the staphylococcus three times, and once the two species together.

Babes also found the staphylococcus aureus in a case of pulmonary gangrene. This micro-organism was associated with a bacillus which produced a general infection and which the author described under the name *proteus lithalis*. The latter appears in the form of small rods, measuring from 0.8μ to 1.5μ, at times growing as filaments. It is a motile, facultatively anaërobic microbe. Subcutaneous inoculation gives rise to considerable edema and causes death in susceptible animals—mouse and rabbit—in two or three days.

In a case of pulmonary gangrene which came under observation of the author in 1900, the morbid manifestations—cerebral symptoms, difficult and slow response to questions, jerky delivery—led him to think of some cerebral localization of the germs which had primarily affected the intestines. The necropsy did not, however, reveal any appreciable lesion of the nerve centres, except a slight serosanguinolent edema of the meninges. Except the intestines, the abdominal organs presented nothing special. To come to the interesting point, however, on continuing the necropsy, the right interlobular fissure was found closed with soft, recent adhesions. In the upper part of the lower lobe of the lung was discovered a large pouch, the walls of which were 2 cm. to 3 cm. thick, containing about 100

[1] Guillemot. Recherche sur la gangrène pulmonaire. Thèse de Paris, 1899.

grams (over 3 ounces) of a fluid exhaling a fetid odor. The sac was perfectly closed. The cavity was crossed by a bronchus, but no opening was found—a fact which accounts for the absence of all pulmonary symptoms.

The data of the necropsy disclose the succession of the pathological events. In order of date, the intestinal incidents were the first, and the pulmonary lesion took its origin in the lesion in the alimentary canal.

The microscopic examination of the fluid showed innumerable bacteria. I shall confine myself to mentioning streptococci, large micrococci, diplococci resembling those of pneumonia, bacilli recalling the anthrax bacillus, and very slender bacilli which were often united in masses.

The various observations briefly reported above show that the foci of pulmonary gangrene contain, as a rule, pneumococci or pyogenic germs associated with saprophytes. The latter may acquire no virulence, as is proved by the negative results at times obtained by inoculating the gangrenous fluid directly into animals and by employing the cultures, or else they become exalted and pathogenic. In the latter instance gangrene is inoculable into animals, and its transmission to man is then conceivable. It is to be noted, however, that while the virulence of these necrosing agents is generally very energetic, their development cannot occur in healthy subjects. In observations upon the contagion of pulmonary gangrene, the contaminated individuals had already been suffering from respiratory affections. Pulmonary gangrene is almost always the result of autoinfection.

The relative frequency of the various causes of pulmonary gangrene clearly appears in the statistics of Hensel,[1] according to whom the most frequent causative lesion is embolism, represented by 20 cases. Of these 20 cases, 9 were pyemic emboli. Then follow the other causes: pneumonia, 14 times; tuberculosis, 11 times; carcinomata in the neighborhood of the lungs, 10 times; bronchiectasis, 5 times; cerebral affections, 5 times; traumatism, 3 times. Lastly, in three other instances, the lesions discovered were a perforation of the esophagus and an abscess of the mediastinum—a focus of actinomycosis—and suppurations of puerperal origin.

Gangrenous and Fetid Pleurisies. Pleurisies, the exudation of which is characterized by a putrid odor, are commonly divided into

[1] Hensel. Beiträge zur Casuistik des Lungenbrandes. Deutsches Archiv f. klin. Medicin, Bd. xli. p. 185.

two groups: gangrenous pleurisies consecutive to sphacelation of pulmonary tissue, and *fetid* or *putrid pleurisies* (*pleurésies ozéneuses* of Dieulafoy), which are produced in the absence of any primary focus in the subjacent organ. In the former case we have to deal with a lesion created by propagation or rather contiguity. The pathogenic germs have reached the pleura after invading the lung and engendering a more or less extensive gangrene in its parenchyma. In the latter instance, the microbes may possibly have penetrated by way of the bronchi and the lungs, traversing these organs without altering them. More frequently they are derived from another region of the organism, particularly from the alimentary canal. Dieulafoy has justly laid stress upon the frequency and gravity of appendicular pleurisies.

This at present classical distinction seems to be in harmony with the etiology and pathological anatomy of the lesions. From the pathogenic standpoint, however, the division referred to is less exact. Whatever the variety under observation may be, the same microbes are always met with—common pyogenic agents associated with saprophytes or numerous aërobic or anaërobic bacterial species. In fact, the pneumococcus, the streptococcus, the staphylococcus, the tetragenus, the colon bacillus, *B. proteus vulgaris*, leptothrix, bacillus of gaseous gangrene, the spirillum of the saliva, the *B. ramosus*, the *B. perfringens*, and the *staphylococcus parvulus* have been found in the pleural fluid.

Gangrene of the Alimentary Canal, Liver, Spleen and Genital Organs. The great number of microbes swarming in the digestive tract explains the frequency of gangrenous lesions observed therein. In most cases, however, gangrenes are superficial and at the necropsy appear under the form of simple ulcerations. On the other hand, true, deep, invading gangrene is quite rare. It is observed especially as a result of hernial or internal strangulations, by preference in intestinal invaginations, as well as a complication of typhlitis and appendicitis, exceptionally as a result of thrombosis of the mesenteric artery.[1] No precise bacteriological examinations have been made in such cases. We are not any better informed as to the superficial gangrenes. The type of the kind is represented by dysentery. Even though the etiological rôle of the ameba be admitted, it is not known what part is played by the various microbes of the digestive canal.

[1] Adenot. Thrombose de l'artère mésentérique inferieure et gangrène du côlon. Revue de médecine, 1890.

The putrid germs may pass from the intestine into the liver and there produce gangrenous abscesses. This is not an uncommon occurrence in dysentery. The primary lesion is sometimes so small as to escape notice, as is proved by an observation of Straus.[1] The liver was the seat of numerous gangrenous abscesses the pus of which was mixed with fetid gases. The spleen also contained a purulent focus characterized by gangrenous odor, including detritus of sphacelated tissue. Numerous microbes, which could not be cultivated, were seen in the sections.

These various lesions of the intestine and its adnexæ may, of course, extend, to the peritoneum.

We have already referred to gangrene of the genital organs, and stated that in the male the external parts may become the seat of gangrene consecutive to genital erysipelas and, in some cases, of spontaneous gangrene characterized by an amazingly rapid course. In the latter case large numbers of streptococci are found associated with anaërobic germs.

Chemical Characters and Toxic Power of Gangrenous Products.

Chemical analyses of gangrenous products have demonstrated that the amount of water increases considerably in moist gangrene. Carbon diminishes, while it is augmented in dry gangrene (Raynaud and Reveil). Albumins are broken up, and yield, on the one hand, leucin and tyrosin; on the other, fatty acids which are, in some instances, sufficiently abundant to impart an acid reaction to the gangrenous fluid. These acids are mostly represented by butyric and valerianic acids which give the focus its fetid odor. There are also found gases, such as sulphuretted hydrogen and ammonia.

These various transformations are evidently related to the multiplication of microbes, and are due, in part at least, to the soluble products or, more precisely, to the ferments secreted by the microbes. This is demonstrated by the investigations of Filehne, Stolnikow, and Escherich, who found in the sputa of patients suffering from pulmonary gangrene a ferment which is similar to trypsin and possesses the property of dissolving even elastic fibres.

Coincidently with the evolution of the local lesions are observed a series of general phenomena of a serious character. Most of these

[1] Straus. Sur un cas d'abcès gangreneux, probablement primitif, du foie et de la rate. Archives de méd. exp., May, 1896, p. 428.

may be ascribed to the microbic products. In fact, we know that the foci almost constantly contain pyogenic cocci, of which we have already studied the toxins, and we have further pointed out that very active substances are secreted by the bacillus of gaseous gangrene and the other necrosing agents.

Some have recently attempted to belittle the rôle of pyogenics, and Veillon, to whom we owe such valuable contributions upon anaërobic bacteria, has contended that gangrene is always due to anaërobic germs. This seems to the author to be an exaggerated statement. The author thinks that along with the strict anaërobics, the influence of which has so well been proven by Veillon and his collaborators, must be classed certain microbes capable of living in the presence as well as in the absence of air. It is also to be noted that putrid decompositions are not always affected by strictly anaërobic microbes. The colon bacillus is a first-class putrefactive agent. To be convinced of this, it suffices to smell the odor of certain cultures. The author would therefore state, in conclusion, that gangrene is a common process to which most varied microbes, either strictly or facultative anaërobics, may give rise. Of these microbes a few are endowed with a high degree of pathogenic power, but this is an exception. Most of them are no more than putrefactive agents incapable of developing in healthy tissues. They multiply only in those parts of the organism which have been altered by previous processes. They are able to induce grave manifestations by virtue of the putrid poisons secreted by them. They are toxicogenetic rather than infectious, and this is the reason the inoculation of gangrenous products often gives rise to no disturbance whatever.

CHAPTER IX.

SEPTICEMIAS AND PYEMIAS.

Definition of Words: Septicemias, Pyemias, Bacteremias, Bacteriotoxemias. Consecutive and Secondary Cryptogenetic Bacteremias. Septicemic Forms of Infections or Specific Septicemias. Agents of Septicemias and Pyemias. Experimental Septicemias and Pyemias. Septicemias of Animals. Hemorrhagic Septicemias. Study of the Epizootic Rhinitis of the Rabbit. Application of Researches of Experimental and Comparative Pathology to Human Pathology. Principal Clinical Characters. Evolution. Importance and Frequency of Attenuated Forms. Variolic Pyemia and Septicemia. Experimental Researches on the Parasite of Smallpox; its Culture and Inoculability.

Definitions and Divisions of Septicemias and Pyemias. Septicemia and pyemia constitute two morbid processes which must be drawn nearer and united under the comprehensive term *bacteremia*. In reality, the pathogenic germ either invades the whole organism without creating special lesions (septicemia), or it locates itself in certain viscera or tissues, and gives rise to the formation of purulent foci (pyemia). In the latter instance a considerable number of small abscesses are generally found at the necropsy occupying the liver, kidneys, lungs, heart, etc.; these are designated by the rather improper name metastatic abscesses.

Bacteremia must be distinguished from bacteriotoxemia in which the pathogenic agent remains localized and gives rise to general manifestations by means of the toxins it secretes. In bacteremia there is general infection; in bacteriotoxemia, intoxication.

Bacteremia, then, includes both septicemia and pyemia. The expression septicemia, created by Piorry, was to be applied to all alterations of the blood produced by septic or putrid substances, whatever their origin. After having been employed in most diverse senses, the term was adopted by bacteriologists who have not succeeded in defining it any better than clinicians. Confusion was further increased when the bacillus of gaseous gangrene was called *septic vibrio*, and the disease induced by it *gangrenous septicemia*. These improper terms led to important errors and nosological confusion. Thus, for example, deceived by these words, some authors believed that septicemia and pyemia should be separated on the

ground of the different characters of their pathogenic agents. According to the expressions used by bacteriologists, septicemia was due to an anaërobic bacillus, namely, septic vibrio, remaining at the point of introduction; pyemia was dependent upon aërobic microbes invading the organism and there producing secondary abscesses.

As a matter of course, a word may be employed in the sense attributed to it by an authority, provided it be well defined. Hence, the term "septicemia" might be reserved for gaseous gangrene and analogous processes. This, however, would be a notable departure from the prevailing tendency, since, logically, it would be necessary to consider all local diseases which kill by intoxication as septicemias, and thus include tetanus, diphtheria, cholera, etc., in this group. In these infections, as in the case of gaseous gangrene, the microbes remain localized at one point, and, as their soluble secretions arouse general reactions, the disease is of a toxic character. This is why these diverse processes constitute a separate group—bacteriotoxemias—and why gangrenous septicemia must be excluded from the group of true septicemias. Thus limited, bacteremias still represent an artificial nosological class; their existence may, nevertheless, be rendered legitimate by the following considerations:

In cases of *septicemia* the microbe is present in every part of the organism; it may often be detected in the blood during life, and always after death. The lesions are those common to all grave infections. The blood is disintegrated and dark in color; numerous ecchymoses are found in the viscera and tissues. Hemorrhages are at times so profuse that the affection deserves to be designated as *hemorrhagic septicemia.* The microscope reveals small vascular thromboses, cellular degenerations, and occasionally embryonic foci, indicating a reactionary tendency on the part of the organism. These foci are limited, however, and are not visible to the naked eye.

At the end of a variable period of time, however, the microbes become localized at certain points of the economy; septicemia then loses the character of a general infection, and visceral localizations become predominant features. The secondary foci then appearing are, in some cases, simple inflammatory lesions; in other instances they undergo purulent transformation. Under these conditions the process might properly be designated as *septicopyemia,* representing a transitional form between septicemia and pyemia.

Pyemias are distinguished from septicemias by the tendency of the infectious agent to localize itself from the beginning in certain

viscera or tissues and there give rise to purulent foci. The germs transported by the blood quickly leave this medium; hence the assertion of some authors that in true pyemia the microbes are found exclusively in the tissues. When they are at the same time encountered in the blood, the process should be held to be septicopyemic. We shall see that this latter distinction is not well founded.

While septicemias and pyemias may produce anatomical lesions, they may also be consecutive to some local lesion. According to their apparent point of origin, two varieties may be admitted. The first is characterized by invasion at once of the entire organism; the portals of entrance of the microbe and the initial lesion are wanting or remain unperceived. The infection is then said to be *spontaneous* or *cryptogenetic*. The latter epithet, introduced by Leube and accepted by Jürgensen, is now frequently employed in Germany. In the second variety, general infection is preceded by a local lesion. Here two events are possible: sometimes the primary focus contains the microbes which subsequently invade the economy, in which instance bacteremia deserves the name *consecutive;* sometimes, on the contrary, the primary focus is the work of specific or non-specific agents which do no more than provide a portal of entrance for the microbe of general infection, in which case bacteremia is said to be *secondary*.

According to the foregoing considerations, we may classify the various types of septicemic and pyemic infections as follows:

Classification of Septicemias and Pyemias.

According to Their Origin.	*According to Their Evolution.*
Primary:	Without special localization (true septicemias).
Traumatic.	
Cryptogenetic.	
Consecutive.	With inflammatory visceral localizations.
Secondary.	With suppurative localizations:
	Septicopyemias.
	Pyemias.

May general infection ever be truly primary or, on the contrary, is it always consecutive to a local lesion, such lesion being in some cases so minute as to escape detection? The latter eventuality is frequently realized. On the other hand, the reality of primary general infections seems to be demonstrated by numerous surgical observations and experimental researches. Clinically, disturbances have been seen to develop in consequence of an accidental, an operative, or an obstetrical wound which seemed in good condition. The same

is true with regard to animals. When an extremely virulent microbe a certain streptococcus, for instance, is inoculated beneath the skin, death supervenes from bacteremia without the slightest local lesion. Furthermore, under a great number of circumstances, the microbes which we carry normally, notably those of the alimentary canal, may penetrate into the economy, and, under debilitated conditions of the system, they may at once induce a general disease. In such cases it is impossible to find a trace of their passage, for no local lesion exists. If it were always possible to determine the mechanism of the infection, occurrences of this kind should be grouped under the name *autobacteremia.*

Consecutive general infections are the most frequent as well as the most important, since they include the great majority of surgical and obstetrical septicemias and pyemias. In this group should also be included certain cases in which the primary lesion is of a medical order, to wit, occupying such parts of the organism as to render operative intervention impracticable. This evolution is met with not only in suppurative lesions, but it is of constant occurrence in the course of the most varied maladies. For instance, when an erysipelas or a pneumonia terminates in death, the infection nearly always assumes a septicemic form. At the necropsy, and even during life, the microbe concerned, be it the streptococcus or the pneumococcus, is found in all the organs and in the blood.

The same evolution may be observed with highly differentiated bacteria. Anthrax is a good illustration. In man, the bacillus gives rise to a local lesion, viz., a malignant pustule. Too often, however, it crosses the barrier opposed to it by the organism and invades the whole system. The patient is then said to have died from anthrax septicemia. It may happen, at least in animals, that even the local lesion is absent, anthrax manifesting itself as a true septicemia.

It is likewise said that such or such an infection assumes a septicemic form in cases in which it evolves without producing its usual manifestations or lesions. Thus, a septicemic form of typhoid fever has been described. It would, therefore, be easy to extend the limit of septicemias so as to include almost all infections, at least certain forms thereof. To avoid the confusion which would result from such a conception, we are obliged to call septicemias those bacteremias which are dependent upon common microbes, and to distinguish those cases in which a well-defined agent has from the first or consecutively invaded the entire organism and behaved as in true septi-

cemia, as septicemic forms or *specific septicemias*. Thus, to take the examples above referred to, we speak of a streptococcic septicemia and a staphylococcic septicemia, whereas, if the question is one of general infection by the *bacillus anthracis*, we employ the expressions specific septicemia or septicemic form of anthrax. By so doing we conform alike to clinical data and to the results of bacteriology.

We believed it proper to sharply separate consecutive from secondary infections. The distinction is equally based upon clinical experience and bacteriology. In consecutive infections it is the same microbe that is responsible for all lesions. Let us take, for instance, a purulent infection consecutive to a phlegmon: clinically, it is the same process that has become generalized; bacteriologically, it is the same microbe, staphylococcus or streptococcus, that is found both in the initial phlegmon and in the metastatic abscesses. Pyemia is then said to be consecutive.

On the other hand, let us take a case of diphtheritic angina. If the patient succumbs to septicemia, as the latter is induced by the streptococcus while the primary agent remains localized in the throat, we say that this septicemia is secondary. It is a second process superadded to the primary. Likewise, the arthrites of gonorrhea may be produced by the gonococcus. This is an instance of consecutive bacteremia resulting from the generalization of the principal infection. In other cases the arthrites are due to an infection superadded by a pyogenic micro-organism which has simply profited by the urethral lesion and invaded the economy; this is a secondary bacteremia.

Bacteriology. The author thought it well to include septicemias and pyemias in one group. While pathological anatomy sharply separates these two processes, clinical experience recognizes a close relationship between them, and bacteriology confirms the results of observation by demonstrating that the same pathogenic agents are concerned in the great majority of cases.

There exist certain microbes which thus far have been met with only in one of the two processes. This restriction, while preventing a complete identification of pyemias and septicemias from an etiological standpoint, is not of sufficient importance to separate the two morbid groups. The most common agents of the two processes are, in fact, streptococci and staphylococci, less frequently the other bacteria to which reference has been made when treating of suppu-

ration, and, lastly, in some cases, more or less well-defined microbes or even simple saprophytes that have acquired an unexpected degree of virulence.

The same agents may cause septicemias in man and in animals. In the latter, however, a great number of species have been met with which thus far have not been detected in man. Moreover, it is easy to produce in animals experimental septicemias, the study of which has largely contributed to the advance of bacteriology. We may, therefore, divide septicemias into two great groups: spontaneous septicemias—*i. e.*, those occurring without any voluntary inoculation—and experimental septicemias. In the former group we may conveniently study the septicemias of man, affecting exclusively the human species, or both man and animals, and septicemias attacking animals only.

Experimental septicemias may also be subdivided into two groups, according as they are produced by microbes derived from living organisms or by saprophytes coming from putrefied substances —air, soil, and water.

The following table will give an idea of the principal bacteria thus far encountered. The list is necessarily incomplete, but its main inconvenience is that it includes identical microbes as distant species. In fact, it is known how difficult it is to determine the bacteria met with. Hence, authors have often held as new such microbes as have already been described, but the biological characters of which have not been sufficiently indicated or have presented variations so pronounced as to render their identification a matter of difficulty:

PRINCIPAL AGENTS OF SPONTANEOUS SEPTICEMIAS.

Of Man and Sometimes of Animals.	*Of Animals.*
Streptococcus.	Bacillus of hemorrhagic septicemia.
Staphylococcus.	Chicken cholera.
Pneumococcus.	Disease of pigeons.
Pneumobacillus.	Disease of canaries.
Proteus hominis capsulatus.	Cholera of ducks.
Proteus vulgaris.	Infectious enteritis of chickens.
Proteus septicus.	Septicemia of rabbits.
Proteus capsulatus septicus.	Purulent rhinitis of rabbits.
Bacillus coli communis.	Septicemia of ferrets.
Bacillus of psittacosis.	Disease of wild animals.
Bacillus pyocyaneus.	Septic pleuropneumonia of calves.
Micrococcus tetragenus.	Contagious pneumonia of pigs.
Bacillus of false anthrax.	Infectious pneumoenteritis.
Bacillus of hemorrhagic septicemia.	B. of septicemia of rats.
Bacillus septicus putidus.	B. capsulatus.
	B. hydrophilus fuscus.

Experimental Septicemia.

Of Animal Origin.	*Of Saprophytic Origin.*
Agents of septicemias of salivary or nasal origin:	Septicemia of Coze and Feltz.
Bacillus salivarius septicus.	Septicemia of Davaine.
Micrococcus salivarius septicus.	Experimental septicemia of mice.
B. crassus sputigenus.	Experimental septicemia of rabbits.
B. smaragdinus fetidus.	Bacillus septicus agrigenus.
B. salivarius canis.	B. canilicolis brevis.
Agents of septicemias of intestinal origin:	
B. cavicida havaniensis.	
B. caniculicida havaniensis.	
B. acidiformans.	
B. leparis lethalis.	
Streptococcus.	

The agents of pyemia are far less numerous. The principal ones are the streptococcus and staphylococcus, to which may be added a special bacillus described by Levy.

Certain more highly organized parasites may be classified with the agents of pyemia: actinomycetes, for example, which induce even in man multiple suppurations, and thus give rise to a true chronic pyemia. The *oöspora farcinosa* and *oidium albicans* are capable of acting in a similar manner. These various pyemias, however, should be considered as specific pyemias. The common pyemias are almost always dependent, in animals as well as in man, upon the habitual agents of suppuration—streptococci and staphylococci.

Experimental Septicemias and Pyemias.

The study of septicemias and pyemias which may experimentally be produced in animals is of great importance in medicine, since it has powerfully served to establish the fundamental principles of bacteriology on solid bases. These experimental maladies may very readily be produced; it suffices to inject into animals saliva or fecal matters, to inoculate putrefied substances, or contaminated water, or to introduce dust beneath their skin. Many experimenters eagerly entered this field of research and described a great number of experimental diseases characterized by septicemic manifestations.

Researches of this kind are, at present, rather neglected; it would be of value, however, to pursue such investigations in order to demonstrate what relationship exists between diseases caused by saprophytes swarming in putrid matters or found in the air, soil, and water, and spontaneous diseases, developing without any experimen-

tal influence. Important data may thus be obtained regarding the distribution of pathogenic agents outside living beings and the possible sources of contamination.

History. We shall not dwell upon the works of the pre-bacterial period; a very full account of them will be found in the highly interesting article of Jeannel.[1] It will suffice to recall that Gaspard was the first to undertake experimental researches upon purulent and putrid infections.[2] The results were verified by Magendie (1824), Trousseau and Dupuy (1826), Leuret (1826), Boyer (1834), etc. In a remarkable work d'Arcet demonstrated that putrid serosities give rise to putrid infections without abscess; that the injections of pus generally cause death without lesions (1842). The pathogenic idea of d'Arcet was developed by Virchow and accepted by many authors; pyemia was considered as a septicemia complicated with embolic migrations. In 1889 Verneuil stated that pyemia is an embolic septicemia and that purulent infection is a termination of septicemia.

The researches of Berard, Castelneau, Ducret, Sedillot, Batailhe, Gamgee, Chauveau, Billroth, and O. Weber established experimentally that putrefied pus induces septicemia without abscesses, while fresh pus gives rise to septicemia or pyemia—a septicemia when a great amount of pus is at once introduced; a pyemia when small doses are injected and the inoculations are repeated several days in succession. The possibility of reproducing in animals the two infectious processes which were known to clinical experience led naturally to investigation of the mechanism of the events. A few authors believed that pus was engendered by the white corpuscles; such was the opinion of Sedillot, Billroth, and O. Weber.

In order, however, to explain the general phenomena and the mode of development of septicemias, another factor was to be taken into account. This factor was first looked for in chemical substances. The toxic theory, which contains a great deal of truth, was further developed by the works of Panum. It is well demonstrated, in fact, that the symptoms observed in infections depend upon toxic substances; but by what mechanism are the latter produced? Pasteur's works, by showing the animate nature of fermentations, led to a search among the infinitely small for the cause or, at least, the start-

[1] Jeannel. Art. Septicémie et pyohémie. Encyclopédie internationale de chirurgie, 1883, t. i. p. 311.

[2] Gaspard. Memoire physiologique sur les maladies purulentes et putrides et sur la vaccine. Journal de Magendie, 1822, p. 1; 1824, p. 1.

ing point of the events. Thus we arrive at the second or microbic period of the history of septicemias.

From 1865 to 1869 Coze and Feltz[1] published a series of researches on septicemia. They succeeded in inducing septicemic conditions by various procedures. Sometimes they introduced putrid substances beneath the skin of dogs and rabbits; in other cases, they introduced blood derived from typhoid fever, variola, puerperal fever, or scarlatina patients. In all instances the animals died, and the necropsy revealed in the blood a great number of microbes, bacilli, cocci, and little chains. These authors must be credited with having developed a fertile method of experimentation and having observed an important result, to wit, the increase of virulence when inoculations in series are made upon animals. This result was shown to be verified by Davaine,[2] who left cow's blood to putrefy for ten days in the month of July, and injected from two to fifteen drops of it into rabbits, with a fatal result. By making successive inoculations, Davaine recognized that on the twenty-fifth passage the blood was virulent in a dose of one-trillionth of a drop or at times even one ten-trillionth of a drop (0.000,000,000.05 to 0.000,000,000,005 c.cm.). He concluded that septicemia is a putrefaction effected in the blood of a living animal by the activity of vibrios.

These results aroused doubt and criticism. Bouley, Vulpian, who had at first been skeptical, repeated Davaine's experiments, and Behbier, as well as Liouville and Colin, recognized their exactness.

The next attempt was made with the view of discovering the characters of the agents capable of causing such accidents. Popoff[3] made a first attempt by injecting into rabbits the yeast of beer and a micro-organism cultivated in the urine. Klebs produced septicemias by injecting cultures of putrefied tissue. Koch,[4] however, should be credited with the first efforts to characterize and specify the various experimental infections. This work, which is very remarkable for the epoch at which it appeared, does not give sufficient information as to the characters of the pathogenic agents, so

[1] Coze and Feltz. Recherches exp. sur la presence des infusoires et l'état du sang dans les maladies infectieuses. Strasbourg, 1866–69.

[2] Davaine. Recherches sur la septicemie et sur les caracteres qui la dissingue de la maladie charbonneuse. Comptes R. Acad. des Sciences, Jan. 25, 1869. Recherches sur quelques questions relatives a la septicemie. Acad. de Médecine, September 17, 1872.

[3] Popoff. Untersuchungen über die Wirkungen der Bierhefe und der in der Pasteurschen Flüssigheit enthaltenen Organismen auf der thierischen Körper. Berlin. med. Wochenschrift, 1872.

[4] Koch. Ueber die Aetiologie der Wundinfectionskrankheiten. Leipzig, 1876.

that, with regard to several of them, it is difficult to determine their relationship with the agents of other experimental diseases and with those of spontaneous infections.

Septicemias of Salivary Origin. Hitherto experimental septicemias were produced by injections of putrefied substances or pathological products. The inoculation of normal organic fluids, however, may produce the same results. In 1881 Pasteur obtained a septicemia in the rabbit by inoculating the saliva of a boy the victim of hydrophobia. Sternberg arrived at the same result by injecting the saliva of a healthy man; he carefully studied the characters of this agent, and Fraenkel demonstrated its identity with the pneumococcus.

At the present time septicemias have been well studied and classified. We shall briefly indicate the characters of the principal types.

The inoculation of the saliva may give rise to several forms of septicemias in animals. The salivary septicemia with pneumococcus is obtained by inoculating the rabbit or, better, the mouse. The animal succumbs in twenty-four or forty-eight hours and the necropsy reveals the easily recognizable encapsulated microbe in the blood and organs.

The *B. crassus sputigenus* of Kreibohrn[1] is an encapsulated bacillus analogous to if not identical with the pneumobacillus of Friedlaender; it differs from it only in that it is not decolorized by Gram's method. It kills mice and rabbits within twenty-four hours.

The *B. tenuis sputigenus*[2] is an encapsulated bacillus, smaller than the preceding one, is stained by Gram's method and readily develops in the various culture media. It is pathogenic for the rabbit and white rat, but not for the guinea-pig and white mouse.

Aside from these septicemias produced by the human saliva, there is one which Fiocca caused with the saliva of dogs and cats. It is due to a small bacillus, which in cultures on potatoes resembles a micrococcus. It is a facultative anaërobic and does not liquefy gelatin. The cultures are pathogenic for rabbits, guinea-pigs, young rats, and mice.

Septicemias of Nasal Origin. Of the septicemias of nasal origin, we must mention that which Reimann[3] has produced with a bacillus found in a case of ozena: the *B. smaragdinus fetidus.* It is a facul-

[1] Flügge. Die Mikroorganismen. Leipzig, 1886, p. 260.
[2] Pansini. Bakteriologische Studien des Auswurfs. Virchow's Archiv, Bd. cxxii., 1890.
[3] Reimann. Inaug. Diss., Würzburg, 1887.

tative anaërobic. Its intravenous or subcutaneous inoculation kills rabbits in thirty-six or forty-eight hours; the necropsy reveals subpericardiac and subpleural hemorrhages. Large numbers of bacilli are seen in the blood and organs.

Septicemias of Intestinal Origin. The genuine microbe of septicemias of intestinal origin is the colon bacillus. A great number of infections attributed to other agents must be looked upon as due to varieties of this microbe, viz., to varieties of B. coli communis and B. lactis aerogenes.

The B. cavicida havaniensis (Sternberg), found in the intestine of a subject dead from yellow fever, seems to be no more than a variety of B. coli. It exerts no action upon rabbits and kills guinea-pigs within ten or twelve hours. On the contrary, the B. cuniculicida havaniensis (Sternberg), obtained under the same circumstances, is a variety of colon bacillus which, as its name indicates, is pathogenic for the rabbit.

The B. acidiformans (Sternberg), derived from the liver of various cadavers, seems to the author to be analogous to the B. lactis aerogenes. It kills rabbits and guinea-pigs in twenty-four hours.

Septicemias and Pyemias of Saprophytic Origin. As has already been stated, Koch had described several infections consecutive to inoculations of putrefied substances. There is, in the first place, the septicemia of mice, caused by the injection of putrefied blood. This affection, which is due to a small bacillus measuring 1μ by 0.1μ, attacks only the house mouse, not the field mouse or rat. By injecting into rabbits an infusion of putrefied meat, Koch produced a new septicemia, the septicemia of rabbits, due to microbes 0.8μ to 1μ in length. Gaffky observed a similar septicemia by injecting the water of Panke into rabbits. The belief is now gaining ground that all these affections depend upon the same microbe as that of chicken cholera.

Sewer water and the soil contain a certain number of septicemic agents, among which are the B. canalicolis brevis and the B. septicus agrigenus. The former was found by Mori in the sewer water of Berlin; it is pathogenic for mice, rabbits, and guinea-pigs, but not for pigeons. The latter microbe, discovered by Nicolaier in manured fields, resembles the bacillus of chicken cholera, but is a trifle longer. When inoculated into the veins it kills rabbits in twenty-four or thirty-six hours. It is also pathogenic for mice.

To sum up, the great majority of diseases experimentally produced

are due to microbes which we find in natural diseases. In most cases the same microbes under different names are encountered, notably the streptococcus, pneumococcus, pneumobacillus, and colon bacillus. Let us add the proteus vulgaris, mirabilis, and Zenkeri, which are so frequently present in decaying matters and the cultures of which give rise to septicemias in animals.

Spontaneous Septicemias and Pyemias of Animals.

Hemorrhagic Septicemias. There exists a group of microbes, designated as *bacilli of hemorrhagic septicemias*, the importance of which is far greater than was at first believed. The type of the kind is represented by the bacillus of chicken cholera. It was soon learned that the microbes of experimental septicemia produced by Koch and Gaffky were no other than the bacillus of chicken cholera. It was later recognized that a great number of affections observed in birds, cows, wild animals, and the hog depend upon microbes analogous to or identical with the bacillus of chicken cholera. The presence of this agent in putrefied substances (Koch) or contaminated water (Gaffky) shows how widely it is distributed and explains the apparently spontaneous development of certain epizoöties.

The bacillus of hemorrhagic septicemia is the agent of at least fifteen diseases that were once held to be different. In some recent contributions, Dr. Lignieres introduces other affections, notably the diseases of dogs and cats and the typhoid malady of horses, and proposes to call the group *pasteurelloses*. Distinctions may be established according to the species spontaneously affected and those which may be infected in laboratories. It is to be noted, however, that the pathogenic action varies considerably with the origin of the virus. For instance, rabbits and chickens, which are so sensitive to chicken cholera, are refractory to the other morbid varieties; while, on the other hand, the guinea-pig, so slightly susceptible to chicken cholera, may easily contract other forms of the infection.

It may, therefore, be questioned whether affections so clearly differing from each other can be classed in one morbid group. They have been grouped for the reason that the pathogenic agents found in these diverse diseases possess analogous or identical morphological and biological characters. Morphologically, they are small, ovoid bacilli measuring 1μ by 0.25μ, and assume, in certain media, the aspect of micrococci or diplococci. They are, with few exceptions,

non-motile. None is spore-bearing. Certain species, like that of chicken cholera, cannot develop without oxygen; most of the other varieties are facultative anaërobics.

The differences existing between the various agents of hemorrhagic septicemia recall those observable in the group of colon bacilli. The comparison is the more interesting as the characters, considered as distinctive, are the same in both instances. These consist in the different appearances of the cultures on potato and in milk, the production of indol, and motility and non-motility of the elements. All these characters, however, are contingent and variable and do not suffice to specify a microbe. The same is true as regards the pathogenic action. The microbe of chicken cholera is extremely virulent for the chicken and for the rabbit, while it is slightly so for the guinea-pig; its inoculation produces nothing more than an abscess in man, the horse, and sheep.

Such are the reasons which, since the works of Hueppe,[1] Baumgarten,[2] Caneva,[3] and Bunzl Federn[4] have led to the creation of the group of hemorrhagic septicemias. We should like to include in this group the epizoötic purulent rhinitis of the rabbit.[5] This affection, of not uncommon occurrence, attacked some of the rabbits of our laboratory in the spring of 1900. We then seized the opportunity to take up the study of this malady.[6]

Epizootic Purulent Rhinitis of Rabbits. The purulent rhinitis starts with an abundant nasal discharge. The animal grows thin and loses appetite. The discharge lasts about a week without any other symptoms, and the affection invariably ends in death. In one case, fatal termination seemed to be hastened by profuse nasal hemorrhages. At the necropsy upon these rabbits, the mucous membrane of the nasal fossæ is found to be the seat of congestion; the trachea, bronchi, and sinuses of the face contain a clear, slightly purulent mucus, and one is at times surprised at the absence of other micro-

[1] Hueppe. Ueber die Wildseuche und ihre Bedeutung fur Nationalokonomie und Hygiene. Berl. klinische Wochenschrift, 1886, p. 753.

[2] Baumgarten. Lehrbuch der pathologischen Mykologie, 1890, p. 489.

[3] Caneva. Ueber die Bakterien der hämorrhagischen Septikämie. Centralb. f. Bakteriologie, 1891, Bd. ix., p. 557.

[4] Bunzl Federn. Bemerkungen über Wild und Schweineseuche. Ibid., p. 787. Untersuchungen über einige Erkrankungen des Schweine. Archiv f. Hygiene, 1891.

[5] There is a very interesting study on hemorrhagic septicemia in the book of Nocard and Leclainche. Les maladies microbiennes des animaux, Paris, 1896.

[6] Roger and Weil. Recherches bacteriologiques sur la rhinite purulente epizootique des lapins. Arch. de méd. exp., July, 1901.

scopic lesions. In certain cases, however, there is a marked splenization in the lungs, even hemorrhages; the organs of the abdominal cavity are congested, and the spleen enlarged. The pathogenic agent, examined in the pus or in cultures, appears in the form of oval elements which might easily be taken for micrococci. They are small, non-motile bacilli measuring on an average 0.6μ to 0.7μ, sometimes 1μ. They are stained with difficulty and are decolorized by Gram's method. Strictly aërobic, this microbe rapidly develops in ox serum gelatin. Its vitality and virulence are well preserved only in the serum of rabbits. Cultures made in this medium were employed in our experiments and enabled us to produce in rabbits a disease analogous to the spontaneous affection by its evolution and lesions.

This disease of the rabbit has been the object of two publications in Germany. The first by date is that of Beck, who isolated a pathogenic bacillus comparable to that of human influenza. Krauss found a bacillus which he believed represented a new species. Our bacillus is not identical with the two preceding ones. Nevertheless, it is quite likely that it is the same parasite assuming somewhat peculiar characters according to various epizoöties.

Human Septicemias and Pyemias.

The preliminary study above presented on experimental and spontaneous septicemias and pyemias of animals will facilitate comprehension of these infections in man.

Many pathologists divide septicopyemias into surgical, puerperal, and medical. It seems to me more rational to take into account both their point of departure and nature. We shall first study primary, traumatic, and cryptogenetic septicemias. They may become manifest at once without any appreciable cause or in consequence of a traumatism or important surgical operation. Dr. Jayle has well demonstrated that a great number of cases considered as instances of shock consecutive to opening the abdomen must be attributed to acute septicemia, commonly due to streptococci. A second group includes septicemias consecutive to a local lesion. If the latter is created by a highly differentiated micro-organism, the septicemia is said to be specific and will not be dealt with here. We are to study only those cases in which the lesion and its consequences depend upon common bacteria, generally of the pyogenic group.

Finally, secondary septicopyemias are those in which the general

infection is induced by an ordinary microbe secondarily engrafted upon a previous microbic lesion.

Bacteriology. The microbes commonly found in human septicemias and pyemias are already known to us: they are chiefly the streptococci, staphylococci, pneumococci, pneumobacilli, proteus and colon bacilli. (See table, p. 249.)

Differentiation of the various microbes found in septicemias from the pneumobacillus of Friedlaender has been based upon the results of inoculations. In fact, it is admitted that the pneumobacillus is not pathogenic for the rabbit. The author's[1] researches, however, demonstrate that its intravenous inoculation gives rise to a fatal septicemia characterized, in a great number of cases, by multiple hemorrhages. This fact, which is contrary to classical opinion, must, I think, be emphatically stated. As a result of intravenous inoculations, there may be observed one of the following three types:

1. Hemorrhagic septicemia with swelling and infarction of Peyer's patches, intestinal hemorrhages.

2. Septicemia, without any obvious lesions, with numerous microbes in the organs and the blood, or only in the organs—*i. e.*, without microbes in the blood, at least so far as microscopic examination reveals.

3. A chronic disease characterized by albuminuria associated with renal alterations; at times by cardiac dilatations and paralyses.

These results seem to authorize us to more closely ally the pneumobacillus with various encapsulated microbes pathogenic for the rabbit. The manifestations observed are also interesting, because they resemble those encountered in man and serve to elucidate their mechanism.

The colon bacillus is very frequently concerned in septicemia. The microbe of psittacosis, which does not differ greatly from this, may be considered as a species intermediary between the colon bacillus and the bacillus of Eberth. It was discovered by Nocard in diseased parrots, and has been well studied by Gilbert and Fournier. These authors have observed an epidemic attacking five individuals in one family. Three were slightly affected; the two others succumbed in eight or nine days. The microbe was detected at the necropsy in the blood of the heart, and proved to be extremely virulent for parrots, mice, guinea-pigs, rabbits, and pigeons. Psittacosis manifests

[1] Roger. Action du bacille de Friedlaender sur le lapin. Soc. de biologie, January 20, 1894.

itself in man by symptoms resembling those of adynamic pneumonias of typhoid fever, with pronounced predominance of nervous perturbations.[1]

Although unable to affirm positively its pathogenic rôle, we should like to note that the *leptothrix buccalis* has at times invaded the viscera. Poncet reports the observation of a patient who succumbed to a putrid infection consecutive to a dental abscess. Quantities of this microbe were found in the metastatic foci and cardiac coagula.

Reference has already been made to the numerous investigations with regard to hemorrhagic septicemias of animals. No less important researches have been pursued with regard to hemorrhagic septicemias of man. It will suffice to mention those of Klebs, Ceci, W. Cheyne, Petrone, Letzerich, Demme, and Hlava. The last-named author has even advanced the idea that hemorrhagic fevers are due to a superadded infection by a hemorrhagiparous bacterium. This opinion will receive notice later in connection with variola. In certain cases of hemorrhagic infection there has been found a bacillus analogous to that of chicken cholera or rabbit septicemia. Tizzoni and Giovannini, Babes, and Kolb have found a similar microbe in purpura hemorrhagica. Babes further asserts that this microbe is present in the most varied infections—septic pneumonia, omphalitis, keratitis, followed by hemorrhagic septicemia, hemorrhagic variola, and septicemia resembling typhus fever. Belfanti and Pescarodo have found the same microbe in a case of tetanus. Sternberg has encountered it in the liver of an individual dead from yellow fever. Lastly, we have found in a case of putrid pleurisy an analogous microbe, present in the exudate with various other bacteria—viz., streptococcus, staphylococcus, and colon bacillus. It was the typical aërobic, ovoid bacterium developing in agar-agar and gelatin, like the microbe of chicken cholera. Its subcutaneous inoculation, even in very small doses, produced in the rabbit a septicemia ending in death within twenty-four hours, while in the guinea-pig there appeared at the point of inoculation a profuse serous exudation, then an abscess which opened in a few days and healed spontaneously. It is evidently difficult to say what rôle had been played by this microbe in the genesis of the symptoms presented by the patient; it is nevertheless interesting to call attention to the rare observations in which the bacillus of hemorrhagic septicemia has been noticed in man.

[1] Gilbert and Fournier. Contribution à l'étude de la psittacose. Académie de médecine (report by Dr. Debove), October 20, 1896.

If we further bear in mind that the microbe of hemorrhagic septicemia may be encountered as a simple saprophyte in the buccal cavity of man (Baumgarten), dog, and cat (Smith), we shall conclude that the microbes constituting this group must play in human pathology a rôle of greater consequence that was at first believed.

Relative Frequency of the Various Septic and Pyemic Agents. Having briefly reviewed the principal microbes which may be found in cases of bacteremia, we must determine the relative frequency of each of them. The most complete study on this subject is that of Canon,[1] whose investigations covered seventy cases. The author divides his results into three categories, according as the process was one of septicemia, septicopyemia, or true pyemia—*i. e.*, pyemia without the presence of microbes in the blood.

In the cases of septicemia, twenty in number, Canon has found chiefly the streptococcus, less frequently the staphylococcus, once the pneumococcus, at another time the colon bacillus, and, lastly, in one case, an unidentified bacillus. These microbes were found in the blood and in the primary focus. In two cases, however, the initial lesion contained both the streptococcus and staphylococcus, but the latter alone entered the blood. These results were secured with blood obtained from the cadaver. Examinations made seven times upon the living subject gave positive results in three instances.

The second group comprises twenty cases of bacteremia with metastatic foci. In eleven patients with various primary lesions Canon found mainly streptococci and staphylococci, once the pneumococcus, at another time a large unidentified bacillus. Out of five examinations of the blood made during life, four yielded positive results.

The author next reports five cases of osteomyelitis. With the majority of German physicians he interprets this affection as a pyemia of the developmental period. It is rather a staphylopyemia, since out of the five cases the *aureus* was found three times, once the *albus*, and once a diplococcus. Examination of the blood during life gave positive results four times. In a last group the report concerns cholelithiasis; the pneumococcus and staphylococcus were found.

[1] Canon. Zur Aetiologie der Sepsie, Pyämie und Osteomyelites auf Grund bakteriologischer Untersuchungen des Blutes. Deutsche Zeitschrift f. Chirurgie, 1894, Bd. xxxvii.

Finally, there remain those cases in which metastatic foci were developed without any microbes being found in the blood. There are cases of pure pyemia upon which Canon does not dwell.

Petruschky[1] has also examined 59 cases and Sittmann 23 cases. From these researches it is seen that the microbes most frequently encountered in bacteremia are the streptococcus and staphylococcus, next comes pneumococcus, and then colon bacillus.

Clinical Evolution. We do not intend to describe the symptoms and lesions of bacteremias; we shall confine our remarks to a few general considerations, the clinical history of these infections having long since been known.

Bacteremias may occur under two quite distinct conditions. Sometimes there is a wound or a previous alteration; sometimes the organism is, or appears to be, normal. The first group includes puerperal, surgical, and certain medical bacteremias, notably those arising in the course or in consequence of eruptive fevers, anginas, and tuberculosis. The second group comprises those cases in which infection may be considered spontaneous or cryptogenetic. Puerperal infections are most frequently caused by the streptococcus. According to Morse, this micro-organism is found in 67 per cent. of the cases. The possibility of infection by the staphylococcus aureus and even by the gonococcus has also been demonstrated.

The fact that the streptococcus is so frequently concerned in puerperal infection has confirmed the old observation of clinicians as to the relationship between this disease and erysipelas. It should not be believed, however, that a puerperal woman suffering from erysipelas is condemned to develop septicemia. The results obtained by us are of a nature to render the diagnosis far less pessimistic.[2] Nineteen patients affected with erysipelas were confined in our wards without the occurrence of any symptoms of importance. The prognosis is not any worse when erysipelas supervenes after confinement. We received nine women under these conditions; all recovered readily.

There is also a category in which puerperal infection appears spontaneously. Although the number of such cases is decreasing with the advance of asepsis, the possibility of autogenic infection may be admitted. The microbes develop owing to a profoundly weakened condition of the organism, and infection is then prepared by digestive

[1] Petruschky. Untersuchungen über Infektion mit pyogenen Kokken. Zeitschr. für Hygiene, 1894.

[2] Roger. Étude clinique de l'érysipèle. Rev. de méd., 1896, p. 236.

disturbances, putrid fermentations in the intestine, or some intercurrent affection, as well as by the retention of placental remains. The last-named incident is of frequent occurrence, and gives rise to putrefactions under the influence of saprophytes; the products thus originated favor infection considerably.

We will not dwell at length upon the causes of surgical infection. In some cases the wound is contaminated with germs, and general infection follows at once. In other instances a local lesion is first produced, which subsequently gives rise to general infection. Lastly, infection may result from traumatism unattended by any wound. Facts of the last category are exceptional. Wagner has reported a remarkable example: it was a case of pyemia consecutive to a fall upon the hip. When, however, bacteremia is consecutive to a wound, it is not at all necessary for the latter to be a large one; serious phenomena have been seen to follow slight traumatism. Landois cites a case of pyemia following a leech bite. It must be acknowledged, however, that infection is favored by all causes that produce severe attrition in soft tissues. Disinfection of such wounds is difficult, and microbes find in contused and altered parts conditions favorable to their development. Finally, with regard to surgical as well as puerperal infections, the dominant etiological factor resides in the transportation of germs by the hands of the operator or by poorly sterilized instruments.

The last group, which also belongs in the domain of surgery and medicine, comprises those cases in which bacteremia is consecutive to an old lesion, for instance, suppurating wounds or deep-seated lesions which scarcely admit of disinfection. It has already been stated in connection with the process of suppurations that, in order to explain generalization, it is necessary to assume a previous modification of the organism, probably through the agency of microbic products originating in the primary focus.

If we now pass to medical affections, we likewise see that there is no constant relation between the gravity of the primary lesion and its tendency to generalization. Cutaneous suppurations, notably those of smallpox, alterations of the tonsils, intestinal ulcerations, lesions of the liver, urinary passages, and lungs, are the most frequent causes of infection.

Lastly, there remains the group of *cryptogenetic septicemias* in which general infection seems to occur spontaneously. This group may be divided into two secondary groups. The initial lesion some-

times remains unnoticed, not having revealed itself during life by any appreciable symptom; it existed, nevertheless, and was found at the necropsy. It may be a visceral suppuration, an intestinal ulceration, an old focus within some gland, etc. There are, however, other instances in which the most searching post-mortem examination reveals no previous lesion—infection has been effected in the absence of any starting point. In certain cases its development may be accounted for by a previous state of general debility. It is highly probable that penetration of microbes into the system occurs constantly, but they do mischief only when, as a result of exhaustion from overwork, or cold, or some other cause, the organism is unable to destroy the germs. It is to be acknowledged, however, that there are cases of infection which defy all explanation—no cause can be found to account for their development.

Infection may evolve as a septicemia without any localization. The disease is characterized by intense initial chills, continued fever, and a grave general state. The prognosis, however, is often less serious than in cases of surgical or puerperal septicemia.

From the beginning or at a later period septicemia may become localized in a viscus. At times localization is not clear, and must be carefully looked for, or it may seem to be of little importance, as is the case when it is expressed by an attack of albuminuria or the development of an erythema. In other instances visceral localization is the striking feature, while the septicemic phenomena tend to amelioration. In such cases septicemia represents a period of transition leading to infectious localization, which then constitutes the disease and develops on its own account. It is not rare to meet with records of such instances in which general infection is scarcely referred to, although it has been the cause of the localization which selects the heart, vessels, lungs, or the liver, and may result in ulcerative endocarditis, arteritis, phlebitis, bronchopneumonia, acute nephritis, or diffuse hepatitis.

These various localizations are simply of an inflammatory nature; in other cases, however, they may be expressed by suppurative lesions; septicemia then terminates in pyemia. It is certainly difficult to say why a septicemic pathogenic agent may sometimes give rise to suppuration. Some authors assume that the purulent function already denotes a certain degree of reaction on the part of the system, and that it may be accounted for by a moderate virulence of the infectious agent. This same explanation has received a more scien-

tific formula. According to Sittmann, septicemia is of a toxico-infectious nature; it occurs when bacteria find in the organism conditions favorable for the production of poisons; in the contrary case the bacteria are in part destroyed, and the proteins of their cadavers excite the formation of pus.

The articular localizations of pyemia had long been confounded with articular rheumatism when Lasègue and Quinquaud individualized them. The latter author has described them under the name arthrito-suppurative disease. The works of Prof. Bouchard and Bourcy have conclusively established the nature of these infectious pseudorheumatisms which sometimes occur in a primary manner and sometimes appear in the course of or subsequently to the most varied infections. What essentially characterizes this clinical type is that the process involves only a small number of joints; the lesions manifest a great tendency to become localized by preference in the knee-joint, to undergo purulent transformation, or terminate in ankylosis. This limitation of the process to a joint contrasts with the tendency of polyarticular rheumatism to affect successively various joints. Moreover, sweating and polyuria are absent in the former instance and, finally, salicylate of soda is useless in such cases.

Pyemia with cutaneous or subcutaneous determinations is less common. In the former case infectious erythemas and purpura develop, with formation of pustulæ and bullæ filled with pus. There is a clinical type in which the eruption of pustules, the so-called pustules of Colles, are produced after an abrupt invasion characterized by chills, fever, and rachialgia. These manifestations subside when the eruption appears. The latter consists of small pustules surrounded by a red, inflammatory zone. At first sight variola may be suspected, but a more attentive examination will enable one to differentiate this subepidermic eruption from the eruption of small-pox.

As an illustration of pyemias with subcutaneous determinations we may cite an observation of Broca: A woman, aged twenty-nine years, while nursing a patient with erysipelas, complained of malaise; ten days later she had chills and then developed multiple phlegmons. Death occurred on the sixteenth day, and the necropsy demonstrated the absence of any purulent focus in the viscera.

Attenuated Forms of Septicemias and Pyemias. The expressions septicemia and pyemia suggest the idea of a serious, commonly fatal process. Along with the acute forms, however, should be classed a

certain number of cases in which the process becomes localized and tends to resolution. The manifestations may even be of an ephemeral character. Traumatic fever and milk fever are nothing but septicemic fevers so benign as to subside in twenty-four or forty-eight hours. The same is true as regards certain urinary fevers of very short duration.

These remarks are also applicable to pyemias. Although the forms in which numerous visceral foci exist are necessarily fatal, there are also benign forms in which localization takes place in some tissue, for instance, in a joint, and in which cure is effected by a surgical operation. Even in grave cases of generalized infections recovery has sometimes been obtained. It is mostly in septicemia without profound cellular lesions that this happy result can be seen. In cases of generalized visceral pyemia attenuation or even destruction of the agent avails nothing; the patient succumbs, not to the infection, but to the visceral lesions resulting therefrom.

Variola, Pyemia and Septicemia.

The relations existing between septicemias and pyemias are clearly evidenced by the study of a specific infection, variola.

The virus penetrates into the organism, probably through the respiratory passages and invades the blood. Then reactionary manifestations of extreme violence appear. If the virus is very energetic it produces profound cellular lesions and marked alterations in the blood. Erythemata, purpura, hemorrhages in the skin, mucous membranes, and principal organs are among the frequent events. The individual succumbs in the absence of any tendency to suppuration. It is a case of genuine hemorrhagic septicemia.

If the virus is less powerful, the expulsion of the parasite may be effected. The organism eliminates it through the mucous membranes and the skin, and papules appear at the various points by which the microbes are rejected. A struggle is begun against the pathogenic agent which results in the formation of pustules. There is no intervention on the part of pyogenic cocci ever present in the mucous membranes and integuments; suppuration is due to the specific agent which thus gives rise to a pyemia with cutaneous determination.

Between the two extreme types there are numerous transitions. In certain cases, in the course of variolar septicemia, the organism makes a last effort which is expressed by the development of a few

irregularly distributed pustules. On the other hand, a suppurating variola may become modified in its progress by the occurrence of secondary hemorrhages. Lastly, there exist some mixed cases of infection in which pustules and hemorrhages make their appearance synchronously.

These facts lead us to the conclusion that the pustules are the result of the struggle against the parasite. When the virus is very active the eruption is not produced; the patient succumbs to hemorrhagic septicemia. In fact, out of forty patients with primary hemorrhagic variola admitted into our wards, none recovered.

In cases of pustular variola, the eruption is intense in proportion to the abundance of the virus. From cases with confluent pustules down to those in which the pustules are extremely rare or altogether absent, there are numerous intermediate degrees. The cases with no eruption are recognized only at the time of an epidemic. An individual who has been exposed to contagion suffers, fifteen days later, from chills, fever, and rachialgia. Four days later the symptoms tend to disappear without the appearance of eruption. Were it not for the etiological data derived from the circumstances, a diagnosis would be impossible. These facts were known to ancient clinicians. Modern hematological researches have demonstrated their reality beyond all doubt by showing in the blood the presence of the special mononucleosis which is characteristic of variolar infection.

The ideas above expressed do not agree with the opinions of certain authors who attribute to secondary infections a primordial rôle in the evolution of variola. Some explain in this manner the purulent transformation; others admit, with Hlava, that hemorrhagic variola is due to microbic association; superadded bacteria are supposed to modify the course and aspect of the disease. It is true that pyogenic bacteria are always found in the pustules, at least at an advanced stage of their evolution, and that the streptococcus is constantly detected in the blood and organs at the necropsy. In cases of hemorrhagic variola this microbe is at times detected in the blood during life. Hence, some bacteriologists considered the streptococcus as the specific agent of the disease and designated it the *variolococcus*. The author believes too much importance is accorded to this microbe, which must be looked upon simply as a superadded agent aggravating the prognosis. He does not regard it as the cause of the suppuration, since pustules may contain no streptococci. He has often examined or sown the pus without being

able to detect any bacteria which could be stained or cultivated by our present methods. In one case blood was drawn one hour before death from the vein of the elbow of a patient suffering from primary hemorrhagic variola, and neither the streptococcus nor any other bacterium was found. Pyogenic bacteria may likewise be absent from even suppurative visceral lesions.

On the other hand, experimentation demonstrates that the pus and at times the blood are virulent. Their inoculation into the rabbit is followed by the development of a fatal disease which, under certain conditions, may be transmitted in series. The blood of the inoculated animals, taken during life, proves virulent, although it is also devoid of bacteria.

Rejecting the bacterial origin of variola, we are led to the question whether this disease is not due to special parasites, and notably to the protozoa that have been described by a few authors.

Microbiology of Variola. Dr. Renaut was the first to point out, in 1881, special corpuscles in the pustules which he held to be parasites and to which he attributed a mechanical action in the formation of the cutaneous cavity. Van der Loeff gave a fairly exact description of these elements and, about the same time, L. Pfeiffer, widening the range of the debate, published a series of highly interesting researches upon the rôle of protozoa in the development of infections and notably in vaccinia and smallpox. Guarnieri inoculated the pus of variola or the fluid of vaccinia into the cornea of the rabbit; a pustule developed, the study of which showed strange figures interpreted by the author as the various phases of the evolution of the parasite. From that time onward various contributions appeared, and now there is general agreement as to the presence of small special elements in the fluids of variola or vaccinia. It was relatively easy to see these corpuscles, but difficult to determine their nature and significance. While the above-mentioned authorities considered them as parasites, others could not see in them anything but simple nuclear detritus. Such was the opinion of Salmon,[1] to whom we owe a remarkable work of experimental criticism on this subject.

From the very beginning of our researches on variola[2] we have

[1] Salmon. Recherches sur l'infection dans la vaccine et la variole. Annales de l'Institut Pasteur, April, 1897.

[2] Roger and Weil. Inoculabilité de la variole humaine au lapin. Soc. de biologie, November 10, 1900. Recherches microbiologiques sur la variole. Ibid., November 17, 1900. Recherches sur le parasite de la variole, Presse méd., November 28, 1900.

noticed these special elements, and we have constantly observed them in both man and inoculated animals.

It is not easy, however, to recognize these special elements. Some of them are very small and do not measure more than 1μ; they may then be confounded with micrococci. The largest elements attain a length of 3μ and simulate leucocytes. They are likewise found in the blood, even in cases of varioloid. They are, however, more numerous in grave cases and particularly abundant in hemorrhagic forms. And yet, even in the latter case, it is often necessary to examine the preparation for a long time and search several fields of the microscope in order to detect a single element. In the hemorrhagic forms the corpuscles are present in all extravasations of blood, in hematoma, and in the urine in the case of hematuria; the necropsy reveals their presence in the various organs, especially in the spleen and bone-marrow.

Without dwelling upon all the arguments which tend to demonstrate that these corpuscles are not cellular detritus, we shall mention two necropsies which we had the opportunity of making at the beginning of our researches. Two pregnant women, one of five and the other of six months, having died from confluent variola, we took the amniotic fluid which, in both instances, was clear and transparent. Microscopic examination showed no leucocytes, but only desquamated epidermic cells originating from the fetus and a considerable number of corpuscles; we had never seen such a great number of them. As the possibility of leucocytic detritus was precluded, it seemed to us rational to admit that we were in the presence of parasites that had invaded the fetuses, in whose bodies a great quantity of them was found, and had contaminated the amniotic fluid. The motility of these elements in the amniotic fluid further confirmed our view. They moved here with sufficient rapidity, while their movement was not clear enough in the pus.

In order to be able to conclusively determine the nature and rôle of the corpuscles, it was necessary to resort to experimentation.

Experimental Variola of the Rabbit. We looked for an animal sensitive to the variolar virus, and we found the rabbit to be such.

If variolar pus free from bacteria and containing corpuscles only is inoculated into a rabbit, the result is usually a fatal disease. If the inoculation is made into the anterior chamber of the eye, a thick exudate generally occurs at the end of twenty-four or forty-eight hours, and heals up in five or six days. In spite of the disappearance

of the local lesion the animal continues to emaciate and dies on the tenth to the twentieth day after inoculation. If the pus is introduced beneath the skin or injected into the veins, death supervenes, as in the previous instance, at the end of two or three weeks.

The disease thus produced differs from human variola. The element which seems to be characteristic—*i. e.*, the pustule—and which only exceptionally is absent in man is seldom observed in rabbits. In three instances we saw a few papules develop on the fourth day in the region corresponding to the subcutaneous inoculation, and then resolve in forty-eight hours. In one instance the eruptions were more profuse, about twenty in number.

It is not without interest to note that, although the variola of the rabbit differs from that of the human adult, it resembles the variola of the newborn. Children born of contaminated mothers succumb to a slow septicemia. At times the eruption is altogether absent; in other cases there are but a few disseminated papules which, like those of the rabbit, become covered with a crust and desiccate without suppurating.

Bacteriological examination frequently reveals in man, as a superadded bacterium, the streptococcus, more rarely the pneumococcus, while in animals a large bacillus is generally found. It is important to remark, however, that in two out of every three cases, no microbe whatever can be detected in the inoculated animals, while the corpuscles are constantly found. These possess the same appearance and characters as in man.

The presence of these peculiar elements establishes a new analogy between human and animal variola. This is not, however, absolutely demonstrative of the parasitic nature of the corpuscles, since it may be argued that the phenomenon is one of special alteration produced in the cells of the organism by the variolar virus. It was, therefore, necessary to follow the development of these corpuscles outside the animal system.

Cultivation of the Microbe of Variola. We first studied what occurs when the blood of the infected animal is placed in the incubator at a temperature of 100.4° F. (38° C.) for twenty-four hours. At the end of this period, microscopic examination showed that the number of the corpuscles was considerably increased. Still the increase was restricted and could not be compared with the rapid multiplication of bacteria.

The next point requiring investigation was whether the corpuscles

which multiplied in the blood taken from the infected animal could equally develop in the blood of normal animals. Starting with the blood of an infected rabbit that had been kept in the incubator for forty-eight hours, we once obtained eighteen successive cultures. The corpuscles readily developed in them, retaining their primary characters, except that they were somewhat larger in size, 2.5μ and at times 3μ.

It seems, therefore, reasonable to conclude that these elements are true parasites. It is hardly necessary to add that we have often assured ourselves that the blood of normal rabbits submitted to the same process never presents such corpuscles.

A last point to be settled by experimentation still remained, viz., the effects produced in rabbits by the inoculation of our cultures.

We made the same experiments as with the pus of variola, to wit, we inoculated into the anterior chamber of the eye, beneath the skin and into the veins, with substantially the same local and general results, including, in some cases, the production of a small number of papules, and terminating in death within a period of fifteen to thirty days.

Conclusions. Such are the results obtained by the experimental study of variola. Although numerous, our observations and researches are insufficient and incomplete. We may, nevertheless, draw some conclusions from the accumulated facts.

As the corpuscles multiply outside the organism, in the blood of infected animals, and even in defibrinated normal or incoagulable blood, there is no logical escape from the conclusion that we have to deal not with altered cells, but a parasite, probably a sporozöon, especially when we remember the fact that these corpuscles are also found in the amniotic fluid.

Although as yet incomplete, our experiments have some practical bearings. The parasites which we studied being invariably present in variola patients, we have been able, according as they were present or absent in cases of doubtful diagnosis, to admit or reject the variolar nature of the disease, and our conclusions were confirmed by the ulterior evolution of the cases. We must remark that variola is not the only infection in which these elements are encountered; similar agents are also found in cases of vaccinia and varicella. This does not necessarily mean that these infections are all due to a unique agent, or that they are to be considered as various forms of the same disease. These results merely indicate the relationship of the patho-

genic agents. Clinical observers have long been able to compare certain eruptive fevers to variola. As is generally the case in such matters, the analogies were first seen. Variola and varicella have for a long time been identified. The identity of variola with vaccinia has long been and is still a subject of controversy. The microbiological study, in its present stage of development, shows rather resemblances; later on it will reveal differential characters.

CHAPTER X.

NODULAR INFECTIONS.

Mode of Development and Signification of Infectious Granulations. Infectious Nodules. Microscopic and Macroscopic Nodules. Glanders. Characters of the Granulations of Glanders; Their Analogy to Suppurative Lesions and to Tubercles. General Considerations on the Bacteriology, Etiology, and Nosology of Glanders. Tuberculosis. Characters of the Tubercle Bacillus. Mode of Propagation of Tuberculosis. Pathological Anatomy of Tubercle. Histogenesis. Tubercular Toxins. Sensitive and Refractory Animals with Regard to Tuberculosis. Tuberculosis of Various Mammalia. Avian Tuberculosis. Tuberculosis of the Gallinæ; its Relation to Human Tuberculosis. Tuberculosis of the Psittaci. Unity of Tuberculosis. Pseudotuberculosis. Study of Bacillary Pseudotuberculosis. Oidiomycosis or Endomycosis. Biology of the *Oidium Albicans;* its Action on Man and Animals. Oidian Granulations. Oidian Toxins. Vaccination and Modification of the Serum in Animals Vaccinated against the *Oidium Albicans*. Infections Produced by Yeasts. Actinomycosis. Characters of the Parasite. Etiology of Actinomycosis; its Characters in Animals and in Man. The Various Pathogenic Streptothrixæ. Infections Due to Mucedinæ and Aspergillus. Relation between Tumors and Infections. Inflammatory Tumors. Experimental Tumors.

The development of microbic colonies often becomes a point of attraction for wandering cells which accumulate in the form of microscopic nodules. These are the infectious nodules, for the knowledge of which we are indebted to Friedrich and E. Wagner. They are considered by many authorities to be accumulations of cells surrounding and circumscribing a microbic focus. This conception is inexact, since such formations may, experimentally, be obtained, especially in the liver, by injection of toxins. I have noted, for instance, that the soluble products of the *B. septicus putidus* give rise to the development of nodules; the only difference lies in the fact that the nodules then appear more rapidly than in animals infected by living cultures.

These nodules are held to be formed by round, indifferent cells, at times designated under the improper name of embryonal cells, which are sometimes supposed to have originated on the spot, sometimes to have migrated from the vessels. Investigations have convinced me, however, that the constitution of these nodules is far more complex and varies according to the disease considered. These productions may be expressed in cytological formulæ exactly

corresponding to those of the blood. Thus in variola[1] the nodules of the liver are constituted by more voluminous mononuclears. Some have a clear nucleus surrounded by a protoplasm which can be deeply stained; others contain a dark nucleus and a variable amount of indifferent protoplasm. These cells are mingled with connective tissue cells. The granular, inconstant cells are, in some instances, quite numerous: these are eosinophilic polynuclears, neutrophilic mononuclears, and a few neutrophilic polynuclears. Thus the same elements are found in the variolar nodules as in the hematopoietic organs, a fact which leads to the question whether these nodules express a defensive reaction capable of arousing a cytopoietic function which seemed to be extinct.

The diseases characterized by granulations establish a transition between pyogenic infections and neoplasms. Certain pseudo-tuberculoses resemble genuine tuberculosis in their macroscopic characters; histological examination shows, however, that, in the former case, the granulation is simply made up of a mass of unaltered round cells.

The history of tuberculosis furnishes a remarkable illustration of the relations existing between suppurations, granulations, and neoplasms. In a certain number of cases Koch's bacillus gives rise to cold suppurations; it acts like a simple pyogenic agent. By a more energetic action, it causes the formation of tubercles, the structure of which is far more complex and characterized by the development of epithelioid and giant cells. It is almost a tumor. In certain animals the neoplastic evolution is complete; in the dog, tuberculosis is expressed by productions presenting the appearance of sarcoma and lymphadenoma. Microscopic examination alone is not sufficient to reveal the nature of these tumors; in order to demonstrate their tubercular origin it is necessary to resort to inoculation.

In the same order of ideas we may cite actinomyces which sometimes produces suppurating foci, and sometimes lesions that have long been confounded with sarcoma.

In fact, it is well known that the most commonplace inflammatory lesions may be followed by the development of a cancer. It is hardly necessary to refer to the transitions which relate simple gastritis to polyadenomata and epitheliomata of the stomach. The line of relationship may thus be followed through these various

[1] Roger and Weil. Note sur les nodules infectieux du foie dans la variole. Soc. de biologie, November 3, 1900.

morbid processes. I had the opportunity to observe an experimental fact comparable thereto. The inoculation of the *staphylococcus aureus* into the thyroid artery gave rise to the development of a true tumor. I by no means wish to affirm the infectious origin of cancer. I believe, nevertheless, that these few examples suffice to show the reason why I place nodular diseases in a separate class forming a transition between purulent infections and tumors.

Now, if we consider the entire group of diseases characterized by granulations or nodules, we find the following in their order of increasing complexity:

Glanders, which is rather akin to purulent infections;
Bacterial pseudotuberculosis;
Mycotic pseudotuberculoses;
True tuberculosis, and
Actinomycosis.

Glanders.

Glanders is a virulent, contagious, and inoculable disease, occurring particularly in the horse, the ass, and the mule, and may accidentally be transmitted to various other animal species as well as to man.

Although one disease by nature, glanders may appear under various clinical aspects.

Biology of the Bacillus. The bacillus of glanders appears in the form of small, straight, or slightly curved rods, with rounded ends. It is non-motile or endowed with simple molecular movements. It is very much like the bacillus of tuberculosis, but is a little thicker, measuring from 2μ to 5μ in length and 0.2μ to 0.5μ in breadth. It is readily stained by various aniline dyes, particularly by alkaline solutions, but is decolorized by Gram's as well as by Weigert's method.

Being a facultative anaërobic, the bacillus of glanders readily develops in the various media employed in bacteriology, provided, however, it is placed at a sufficiently high temperature—*i. e.*, at 98.6° or 100.4° F. (37° or 38° C.). A temperature of 131° F. (55° C.) destroys the culture. According to Babes, the bacillus taken from man or the horse does not develop except upon potatoes or in bouillon; it can grow in agar-agar only after it becomes habituated to these media.

The bacillus of glanders can hardly resist the causes of destruction —exposure to air, sunlight, and heat, putrefaction, etc. The secre-

tions of glandered animals rapidly lose their virulence; the pus thinly spread and placed in a confined enclosure becomes inactive at the end of two days, while in the central parts of an organ the virulence may persist for twenty-six days (Cadéac and Mallet). The cultures resist longer, for a period of three or four months (Loeffler).

Animals Sensitive or Refractory to Glanders. The animals most liable to contract glanders are the horse, the ass, the mule. Sheep and goats also contract it easily, even spontaneously. The bovidæ are completely immune.

An ulcer which extends a little and then cicatrizes and heals is observed at the point of inoculation in the dog. The cat is highly sensitive to glanders; at the end of eight days its articulations are invaded, and it often succumbs within two weeks (Lisitcyn). The disease has also been observed in wild animals nourished in menageries with contaminated meat.

Among the small animals we will cite the guinea-pig, which has a pronounced receptivity. The rabbit is far less sensitive than the guinea-pig. With the various species of mammalia, inoculation into the nerve centres offers a very sure procedure for communicating glanders. Success is thus obtained, even with refractory animals; while in those which are susceptible, a disease with a particularly grave and rapid evolution appears, and the virulence of the bacillus is found to be exalted.

Birds are very slightly sensitive to glanders; they might even be said to be refractory, excepting the pigeon, the immunity of which is incomplete.

Etiology. It was for a long time admitted that glanders may originate spontaneously, at least in the horse. At present it is known that this disease cannot occur except by contagion, either through *direct inoculation*, or through *infection*. It is, nevertheless, certain that a predisposition is created by a great many causes—fatigue, bad nourishment, defective hygiene, etc.

Man hardly ever contracts the disease from any other animal than the horse; it is, therefore, conceivable that it should be rare among women; of the latter sex Bollinger finds only 6 out of a total of 120 cases.

Since glandered horses are now being slaughtered, the frequency of the disease has been rapidly declining. The persons affected are naturally those working about horses—hostlers, veterinarians, farmers, and the like.

In some instances the disease has been communicated by biting (H. Landouzy). The result is not always positive, and everyone remembers that Cl. Bernard experienced no disturbance after being bitten by a glandered horse in the course of his experiments.

It has even been admitted that the virus at times may penetrate through the intact skin. The experiments of Babes tend to support this view. This author has seen a few guinea-pigs contract the disease after a salve containing virulent bacilli was rubbed into the healthy skin. Penetration is effected through the cutaneous glands. Arrazat reported an observation in which glanders caused death in ten days, and no wound of inoculation was discoverable. It follows from Nocard's investigations, however, that the absolutely healthy skin does not allow penetration—rubbing practised upon three asses remained ineffective. Operating in the same manner upon fifteen guinea-pigs, this author found that only two contracted the disease, which latter result he attributes to the presence of such abrasions as may easily escape detection.

The mucous membranes may similarly serve as routes of penetration. There are on record several observations in which horseshoers contracted the malady by drinking from the same pail as their horses, or wiping their noses with the rag which had been used to cleanse the nostrils of the diseased animals.

The ingestion of infected flesh has communicated the disease, the bacilli penetrating through the buccal or intestinal mucous membranes. Bollinger affirms that the respiratory apparatus is another portal of entrance, especially in those cases in which general symptoms precede local manifestations.

Pathological Anatomy. The granulation of glanders occupies an intermediate position between suppuration and tubercle. In acute cases it resembles rather suppurating lesions; in chronic cases it is analogous to tubercular lesions.

The histological study of glanders has chiefly been made upon lesions experimentally produced. The best descriptions are those given by Baumgarten, Leclainche and Moutane,[1] and, above all, by Leredde.[2] The first phenomenon is represented by an intravascular accumulation of polynuclear leucocytes; the latter seize upon the bacilli and arrive in such large numbers that they obstruct

[1] Leclainche and Moutané. Etude sur l'anatomie pathologique de la morve pulmonaire. Annales de l'Institut Pasteur, 1893.

Leredde. Etude sur l'anatomie patholog. de la morve. Thèse de Paris, 1893.

the capillaries in which they accumulate. Thus is constituted an embryonal nodule. The cells then undergo degeneration, their nuclei break up, and their protoplasm becomes caseous. The bacilli thus liberated are taken up by the vascular endothelial cells, which become tumefied. If the evolution continues, new leucocytes assemble around the central caseous mass.

In chronic cases mononuclear leucocytes take part in the process. A sclerotic tissue develops which may be composed of small, caseous masses and giant cells formed at the expense of mononuclear leucocytes. Owing to these cells, the histological constitution of the lesion resembles the tubercular process.

This brief description shows that the nodule of glanders is essentially formed of wandering cells: first, polynuclear; subsequently, mononuclear. Contrary to the opinion of Baumgarten, who attributed to them the main rôle, the fixed cells of the tissues play a very limited part in the process.

Tuberculosis.

The definition of tuberculosis[1] is at present furnished by the pathogenic conception. It is the disease, or rather all the lesions, produced by Koch's bacillus. The knowledge of the pathogenic agent has made it possible to trace a series of apparently dissimilar manifestations to their true cause and to demonstrate the relationship existing between the tuberculosis of man and that of animals.

Biology of the Bacillus. It is difficult to obtain a first culture of tubercle bacillus. Either the organs of a guinea-pig inoculated with human tuberculosis are taken as a point of departure, or, as Koch and Kitasato have proposed, a particle from the central portion of a mass of sputum is used. The cultures grow better in gelatinized serum than in any other medium. At the end of ten or fifteen days colonies appear which soon assume the form of well-isolated, whitish or yellowish masses, composed of dry, roughened pellicles. In successive cultures the masses coalesce to form dense and thick membranes.

The tubercle bacillus is affected in a peculiar way by coloring substances. Everyone knows the procedure of Ehrlich which enables us to distinguish this bacillus from all other microbes except

[1] *Tuberculosis, tubercle:* Latin, *tuberculum,* derived from *tuber,* tumor. Both *tuber* and *tumor* are formed from the Sanscrit radical *tu,* to grow.

that of leprosy. This procedure has undergone many modifications; all the proposed methods, however, are based upon the following fact—the microbe is with difficulty impregnated by the aniline dyes, but once the dyes penetrate it retains them powerfully and resists decolorization by dilute acids.

The bacillus appears in the form of small rods, usually measuring from 3μ to 4μ in length and 0.3μ to 0.5μ in breadth; they are straight or slightly bent, at times assuming the shape of an S, or curved at one extremity. Their protoplasm is sometimes homogeneous, at other times formed of small ovoid or round grains. In their interior are often observed colorless, oval vacuoles which have, it seems, sometimes been mistaken for spores.

Until recently the agent of tuberculosis had been classed among the bacilli. In 1884, Petrone, impressed by certain morphological characters of the microbe, thought that it should be classed between the micromyces and schizomyces. This opinion attracted no attention. Metchnikoff showed, however, that the bacillus sometimes presents elongated, filamentous forms bearing terminal or lateral enlargements. He finally pointed out the important fact that the filaments may be divided. Maffucci argued that these various phenomena are observed only in cultures of avian origin; and this was then employed as an argument in support of the dualistic theory of tuberculosis. It is at present known that the same forms, though with some difficulty, may be obtained with human tuberculosis, and, according to recent investigations, it seems certain that the bacillary form of Koch's microbe is but a temporary, transitional one, and that this parasite must be looked upon as a plant of relatively higher development, belonging, with the actinomyces, to the group of streptothrixæ or oöspora. It would, therefore, deserve the name *oöspora kochii* or *tuberculomyces*. (C. Jones); it might be called *tuberculomyces hominis* or *T. avium*,[1] according as the microbe is of human or avian origin.

It is not simply for theoretical interest that we dwell upon these results; they enable us to correlate various pathogenic agents which arouse comparable reactions in the organism. In fact, clinical experience had beyond all doubt recognized the relationship between actinomycosis and tuberculosis; it is, therefore, important to point

[1] Coppen Jones. Ueber die Morphologie und systematische Stellung der Tuberkelpilzes. Centralb. f. Bakt., Bd. xvii., 1895. Ueber die Nomenklatur der sog. Tuberkelbäcillus, ibid., 1896, Bd. xx.

out that their pathogenic agents belong to closely allied botanical species.

The tubercle bacillus presents a very strong resistance to various destructive agents. When dried, it preserves for a long time its noxious properties, especially when the surrounding temperature is low. Thus, according to Pietro, it remains virulent for nine or ten months at 77° F. (25° C.), for two months at 86° or 95° F. (30° or 35° C.), and for one month at 122° F. (50° C.).

According to Cadéac and Mallet, fragments of tubercular lung buried for one hundred and sixty-seven days produced tuberculosis when they were inoculated into animals; beyond this period they gave rise to septicemia; pieces of the same organ left in water had not yet lost their virulence at the end of one hundred and twenty days.

The tubercle bacillus is rather sensitive to the effect of heat; it is killed by ebullition of a few minutes; when dried, it does not resist the action of hot-water vapor. According to Galtier, however, it can endure a temperature of 140° F. (60° C.) for twenty minutes, and one of 158° F. (70° C.) for ten minutes. Ebullition kills it in five minutes (Sormani). The rays of the sun exert the most destructive influence and kill it most rapidly (Koch).

Etiology. The contagium of tuberculosis may be transmitted from animals to man, from man to animals, from animal to animal, and from man to man.

The contamination of man by animals raises several problems of interest. In fact, it must first be questioned whether tuberculosis is similar in all the animal species. If such is the case, as is now generally admitted, is it dangerous for man to ingest the flesh, viscera, milk, and other products of tubercular animals? The muscles seem to have very little, if any, virulence. The milk, as has already been stated, seldom contains bacilli, except in cases of mammary tuberculosis. This source of danger, therefore, although real, is not so great as was once believed, since mammary tuberculosis is rare. Bang has observed only seven cases of mammary tuberculosis in Copenhagen in the course of a year; in France it seems to be still less frequent.

Among the products which are said to have transmitted tuberculosis, we may mention vaccine lymph. Since animal vaccination has come into universal use the question has acquired particular interest, the more so since Toussaint succeeded in inoculating tuber-

culosis through the agency of this fluid. This result has not been confirmed, and the experiments of Lothar-Mayer, Straus, Chauveau, Josserand, and Nocard demonstrated that the bacillus is not found in the vaccinal fluid of either bovidæ or man.

Finally, the dissemination of the bacillus through the urine of dogs must be taken into account. Tuberculosis, which is not rare among these animals, often involves the kidneys, and, in this case, the agent passes into the urinary secretion.

The transmission of tuberculosis of man to animals has been demonstrated by a great number of examples.

House animals such as dogs, cats, birds and, notably, parrots are usually contaminated.

That transmission of tuberculosis does occur from man to man and between animals of the same species is a truth demonstrated beyond all possible doubt.

Flies may carry tubercle bacilli (Spillmann and Haushalter), but they disseminate rather than directly inoculate the virus. The bacilli may likewise remain virulent for a long period in the interior of earth-worms (Lortet and Despeignes).

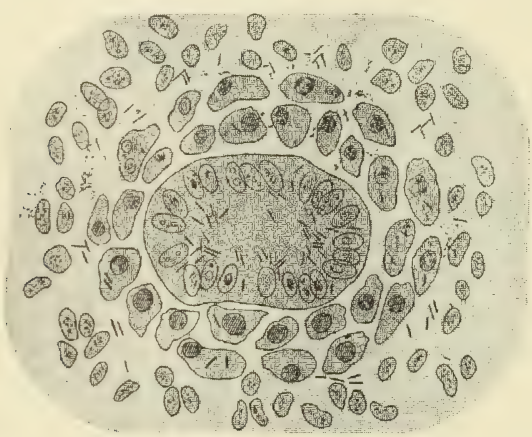
Pathological Anatomy. Tubercular lesions assume two principal forms: they may appear in the form of *granulations*, which are peculiarly characteristic when examined in the serous membranes. They are small, hard, non-enucleable nodules, often surrounded by a red, vascular zone. Their size varies from 0.5 mm. to 2 or 3 mm.; they are at first translucent, but subsequently become opaque and yellowish at their centres. They sometimes present rounded, gray or yellow, isolated masses the size of a pea, a hazelnut, or even a walnut (*Laennec's tubercles*), or they may form opaque deposits infiltrating the tissues (*caseous masses*). In both instances the lesion is essentially composed of granulations which cannot be recognized with the unaided eye.

Alongside with these two principal types must be placed certain alterations which, at first sight, appear absolutely different. Many scrofulides, cold abscesses, lupuses, synovitis with riziform grains are of tubercular nature. The same is true of certain cases of pleurisy, although examination of the lungs does not seem to reveal the presence of any specific lesions.

It may then be asked on what ground are such morbid manifestations held to be tubercular? At the present day, the presence of Koch's bacillus seems to be sufficient to affirm the nature of the

alteration. For some time past, however, histological investigations have considerably extended the domain of tuberculosis. The criterium is no longer the tubercular corpuscle of Lebert, but the presence of a giant cell or a peculiar arrangement of various cells designated under the name *elementary tubercle* or *tubercular follicle.* No doubt the specific character of this lesion is not absolute, and more or less similar alterations may be encountered where there is no tubercular infection. Nevertheless microscopists must be credited with having supplied a powerful argument in support of the unity of tuberculosis and having included with this disease diverse lesions which really belonged therein.

Fig. 6.



Schematic tubercular follicle, showing the three classical zones and the distribution of bacilli.

Let us, therefore, investigate the constitution of a tubercular follicle, and, to this end, let us suppose an ideal elementary tubercle, ignoring the tissue in which it has developed and the surrounding alterations which it may have produced.

What peculiarly characterizes the tubercular follicle is not such or such cellular elements, but the mutual arrangement of the various elements of which it is composed.

Theoretically, according to the conception of Koster, Schuppel, and Friedlaender, the tubercular follicle is formed of three zones (Fig. 6) at the centre, a giant cell, the *Riesenzelle* of German authors; around it, epithelioid cells, and at the periphery an area of embryonal cells.

The *giant cell*, held by Schuppel to be characteristic, is composed of a mass of protoplasm containing twenty, or thirty, or more nuclei, situated at the periphery of the cell, where they form a crown or a crescent. The cell itself is rounded, irregular, flat or spherical in shape, often provided with ramified prolongations. The nuclei of the giant cells are commonly oval and nucleolated; in some cases they are elongated and sinuous, or may even present the form of a Z. Finally, when greatly magnified, there may be seen in some of the cells karyokinetic figures in connection with indirect division of the nuclei. The aspect of the nuclei and their arrangement in the form of a peripheral crown enables one to differentiate the tubercular giant cell from myeloplaxes and sarcomatous giant cells.

The middle zone is composed of large epithelioid cells; the nuclei are rounded or oval, and the protoplasm is abundant and somewhat granular. These cells often contain one, two, or more bacilli; they seem to perish when the parasites become more numerous.

The peripheral cells are simple *embryonal cells*, presenting nothing particular. They are very numerous and pressed one against another. They appear in the form of rounded elements, measuring 4μ to 9μ, and are remarkable for the large size of their nuclei and the scantiness of their protoplasm. In the midst of these cells are found a few fusiform elements which represent a more advanced stage of cellular development.

The elementary follicle is not always constituted in such a perfect manner as above described. At the beginning of the process all that is found is a collection of round cells; at a more advanced period the epithelioid cells may be wanting and the lesion may consist simply of a giant cell surrounded by embryonal elements.

The tubercle is a *non-vascular* production. This is a feature of great importance. At the start, while there is nothing but a simple mass of cells, some permeable vessels may yet be found; but subsequently they become obliterated and disappear; their lumina are occupied by a granular coagulum of fibrin, imprisoning in its meshes white corpuscles accumulated along the inner walls. This vascular obliteration has been variously explained. Some authors have assumed a compression of the vessel (Rindfleisch), others a coagulation of the blood (Chauveau), and still others a primary alteration of the wall—an endocapillaritis (H. Martin).

About the irritated point the vessels dilate and send out prolongations, which are but short-lived.

Histogenesis of Tubercle. The methods of investigation have been quite different before and since Koch's discovery. During the period that may be designated as prebacterial, very exact and detailed descriptions were given of the pathological anatomy of the tubercle. When the specific germ of the disease was known and cultivated it became possible, by inoculating it into animals, to observe day after day the development of the tubercular neoplasm, without running the risk of regarding accessory and secondary processes as essential, or considering as specific such alterations as are common to other diseases.

The importance of lymphatic elements in the genesis and constitution of tubercle was noted from the very beginning of researches. Virchow and his disciples class it with lymphomata. Klebs and Köster think it takes origin in the lymphatic capillary networks. Wagner emphasizes its structural analogy to lymphatic glands (cytogenic tuberculosis). H. Martin and Kiener compare it to the milky patches of the omentum.

Histologists sought for a specific element that would enable them to distinguish tubercle from similar neoplasms; and such were thought to be the giant cells and the absence of vessels in the tubercle.

It was not long, however, before new contributions demonstrated that giant and epithelioid cells are in nowise specific. Heidenhain, Weiss, Baumgarten, and Ziegler produced these elements by inserting foreign bodies into the subcutaneous cellular tissue. Laulanié observed in the cat granulations which presented the appearance and structure of tubercle and were caused by the strongylus vasorum, Hip. Martin produced pulmonary granulations by intravenous inoculation of inert powders.

While discussing the diagnostic value of giant and epithelioid cells, the authorities endeavored to discover the mode of formation of these elements. Langhans suggested two possible events: either the giant cell develops at the expense of one altered cell, or is formed by the union and confluence of several. According to Köster, it results from the proliferation of the vascular endothelium; according to Ziegler it develops at the expense of leucocytes, while Shuppel holds it to be due to the hypertrophy of one migrated white corpuscle followed by alterations in the bloodvessels. This vascular origin, while admitted by Cornil, was doubted by Malassez. Charcot and Gombault contended that the giant cell resulted from fusion of many.

Such were the opinions of authors concerning the histogenesis of tubercle when, in 1882, the discovery of the tubercle bacillus by Koch brought accuracy to our knowledge of tuberculosis. The specific element, which pathological anatomy had failed to furnish, was found out by bacteriology.

From that moment two principal theories have been advanced. According to some, the tubercular neoplasm is composed solely of cells that pass out of the vessels to ingest the bacilli; the tubercle is a superadded production developing at the expense of protective cells that are attracted toward the point attacked. Others assert that it is formed of the constituent cells of tissues (epithelial cells, fixed cells of connective tissues, vascular endothelium, etc.), and that it is to be attributed to the transformation of pre-existing elements normal to the parts.

Among the advocates of the former theory is Koch. The bacillus ingested by the wandering cell is transported by it into the organs, and Koch is not far from believing that the same cells give origin to both the epithelioid and giant cells. While Koch hesitates, Metchnikoff is positive. According to the latter authority, the phagocytes pick up and digest the tubercle bacillus. Moreover, the giant and epithelioid cells which he studied in a small rodent, the spermophile, into which he inoculated avian tuberculosis, also have phagocytic properties. The latter statement is contested by a number of authorities. Gilbert and Girode, as well as Yersin subsequently proved that tubercle develops at the expense of wandering cells. Borrel, studying the histogenesis of tubercle in the lung and kidney by means of inoculations of cultures of human tuberculosis, saw the bacilli ingested by polynuclear leucocytes: the latter, however, died rapidly and were replaced by mononuclear leucocytes which in their turn seized upon the bacilli and were transformed into epithelioid and giant cells. Josué, inoculating cultures of human or avian tuberculosis into the bone-marrow of rabbits, discovered the same process and created in this animal lesions which are circumscribed in the case of human and diffuse in that of avian tuberculosis.

The advocates of the formation of tubercle at the expense of the fixed cells of tissues are also supported by experimental investigations. Baumgarten, who is an enthusiastic defender of this theory, inoculated fragments of tubercular substance into the anterior chamber of the eye of a rabbit, and saw the fixed cells divide by karyokinesis, giving rise to epithelioid and giant cells. The intervention

of the leucocytes is secondary; they invade the neoplasm already constituted by the elements which originate by indirect division from the pre-existing tissue cells. Tubercle is formed in all organs in a similar manner. Baumgarten, who rejects phagocytosis, asserts that the bacilli are not ingested by the cells. Kostenitch, Volkow, and Straus are also advocates of the theory of the formation of tubercle at the expense of fixed cells.

As to the giant cell, it is believed by some to be formed of one cell. Under the influence of an irritation too weak to bring about its division, its nuclei proliferate and remain enclosed in the hypertrophied and undivided protoplasm (Koch, Weigert, Baumgarten). Others contend that the giant cell is produced by the coalescence of several cells, or by the penetration of leucocytes into the masses of degenerated protoplasm, or by these two processes simultaneously (Arnold, Yersin, Borrel, Kostenitch and Volkow, Josué).

We are thus confronted by two theories as to the histogenesis of tubercle; both are supported by well-observed experimental facts. It is therefore to be assumed that both contain some truth and it may then be asked whether they cannot be harmonized. Josué remarks that, under the name of fixed tissue cells, some have confounded the fixed cells of connective tissue, which certainly play a phagocytic rôle, and the epithelial cells. In his opinion, the mesodermic cells—the leucocytes, the fixed cells of connective tissue—ingest the bacilli, but the toxins secreted by the microbes may act upon the surrounding epithelial cells and produce in them epithelioid degeneration. Accordingly, from a histological standpoint, all cells participate in the formation of tubercle; but as far as the fight against the invading germ is concerned, the principal rôle devolves upon the mesodermic cells.

On the arrival of the bacillus, polynuclear leucocytes undertake to ingest it, but they rapidly perish. Then mononuclear leucocytes and connective tissue cells seize upon the germ. Two events are then possible. The organism may immediately triumph, and the tubercle is not produced, or the bacillus may be victorious, and then two successive phases supervene: in the first, the cells are transformed into epithelioid elements and a tubercle is produced; in the second phase, the tubercle undergoes caseous degeneration. Even at this stage of evolution the organism may triumph: if the numerous leucocytes surrounding or penetrating the focus remain powerless, there is another process capable of circumscribing the lesion and of

killing the bacillus imprisoned in the products of its own creation—viz., the process of sclerosis invading the tubercle.

Thus far we have dealt with the local manifestations of the bacillus. Its action is not, however, limited to the point at which it comes in contact with the tissue cells, as may be proved by a study of the modifications occurring in the marrow of bones in the absence of all osteomedullary localization. In fact, Josué has recognized that when tubercular lesions exist at any point of the organism a profuse cellular proliferation occurs in the bone marrow. The modifications of this tissue, with reference to the defense of the organism, are equally observed in man and in rabbits which have been inoculated in regions far from bones or subjected to subcutaneous injections of tuberculin.

Evolution of Tubercle. After having studied the structure and mode of formation of the elementary follicle, it is easy to comprehend the development of granulations, of tubercles properly so called, and of caseous masses.

Gray granulation is commonly formed of several tubercular follicles. Wagner and Charcot admit, in complex follicles, as many simple follicles as there are giant cells. *Tubercles*, properly so called, which are larger than gray granulations, are essentially made up by the union of several elementary tubercles, but the central part undergoes a modification designated as caseous degeneration. At the periphery are found numerous embryonal cells similar to those observed in the external zone of the follicles. The middle zone is remarkable for the presence of giant cells forming a crown around the central degenerated mass. This agglomeration, therefore, possesses a certain individuality. It does not represent, juxtaposed, independent follicles each undergoing degeneration; we are in the presence of a true pathological unity the centre of which degenerates.

The foregoing statement with regard to tubercle may be applied to tubercular *infiltration*, which is characterized by confluent granulations connected by means of embryonal cells. According as the mass is made up of granulations or of caseous tubercles, the condition is known as gray or yellow infiltration. As Prof. Grancher states, every tubercle is composed of two zones—a central caseous zone and a peripheral embryonal one. A closer study of the evolution of the lesions shows that a tubercle is liable to two forms of degeneration —fibrous and caseous.

Caseification is preceded by a stage which Prof. Grancher designates as *vitreous degeneration:* the giant and epithelioid cells lose their nuclei, become vitreous, homogeneous, and coalesce; thus a translucent mass is formed with fissures imparting to it the appearance of an irregular mosaic. This peculiar substance looks somewhat like amyloid substance, but does not manifest its reactions. The translucent mass soon becomes opaque. This is caseous transformation, in which cellular elements are no longer recognizable; the bacilli seem to share the fate of the animal cells; there are very few of them to be found. This caseous transformation, which has long been regarded as specific, may be wanting in man and particularly in animals. On the other hand, it may be encountered in various other pathological conditions, notably in syphilis.

The caseous mass softens, especially when it is communicating with the exterior; it may undergo a purulent transformation, resulting from contamination by pyogenic bacteria.

In other instances the tubercle undergoes a fibrous metamorphosis; this is a tendency toward recovery. Tubercle is transformed into a hard nodule composed of a homogeneous fibrous tissue, including a few atrophied round cells. Vessels develop in the embryonal zone in which giant cells are still found. At certain points the caseous substance becomes encysted; at times it is absorbed. Finally, tubercle may become infiltrated with calcareous salts and undergo pigmentary transformation.

Action of Tubercular Toxins. The tubercle bacillus is capable not only of producing tubercles, but it may likewise produce fatty, hyaline and amyloid degenerations. The sclerotic process which it excites may become preponderant, leading to cirrhoses, especially appreciable in the liver, and it may be encountered in other parts of the organism; the author has shown its occurrence in the muscles, and Dr. Tessier has proved its importance in connection with the heart.

The phenomena of degeneration seem to be due to secretory products of the microbes (Maffucci, Grancher). As to the tubercles, they are produced by a reaction of the system against the bacillus—*i. e.*, the substances contained in the body of the bacillus. The intervention of the living micro-organism is not necessary. The experiments of Prudden and Hodenpyle, Straus, Gamaleia, and Vissman demonstrate that injection of thick emulsions of dead cultures of tubercle bacilli into the veins of animals may produce extremely numerous granulations containing dead bacilli which can be stained by the

usual methods. This necrotuberculosis, to use an expression employed by Drs. Grancher and Ledoux-Lebard, is characterized by considerable emaciation and a cachexia ending in death. The necropsy reveals tubercular granulations, particularly abundant in the lungs and remarkable for their tendency to undergo fibrous transformation and for the absence of caseation. Straus and Gamaleia, however, have seen the centre of such tubercles become caseous, as under the influence of living bacilli. Schweinitz and Dorset admit that the necrosing substance is a definite body having the formula $C_7H_{10}O_4$, and that it is found in culture fluids. The bodies of the bacilli contain an albuminoid substance which is antagonistic to the preceding one; it produces hyperthermia, while the other lowers the temperature, and it is sclerogenic instead of being necrogenic.

A series of experiments pursued by the author demonstrate that special toxic substances are contained in the tubercular tissue itself. In most cases he employed extracts of tubercular glands of cattle and dogs or the liver of tubercular guinea-pigs, either pure or mixed with substances capable of modifying their action. It was thus learned that tubercular tissues contain substances more noxious for the rabbit than the guinea-pig. The emaciation caused in the rabbit is more pronounced and lasts longer.

Inoculability of Tuberculosis. There is hardly a mammalian altogether refractory to tuberculosis. Nearly all may contract it spontaneously or by inoculation. In laboratories the animals most operated upon are the rabbit and the guinea-pig. With the latter animal inoculation is successful, no matter by what route the material is introduced—whether into the subcutaneous cellular tissue, the pleura, the peritoneum, or the anterior chamber of the eye.

As in the case of other infections, the number of bacilli introduced must be taken into account: the greater the amount of virus introduced the more rapidly the disease develops.

The researches of Bollinger and Gebhardt demonstrate that dilution of tubercular substances may render them inoffensive: contaminated milk loses its virulence if diluted to $\frac{1}{150}$ or $\frac{1}{100}$. Animals resist when they swallow 2 c.cm. of tubercular sputum diluted to $\frac{1}{8}$. If, however, inoculation is made beneath the skin or into the peritoneum, it must be diluted to $\frac{1}{100000}$ in order to become inoffensive.

Hischberger, Gebhardt, and Wissokowicz have also demonstrated that rabbits resist amounts which are fatal for guinea-pigs; in the

latter animals tuberculosis develops when a particle of sputum containing 820 bacilli is inoculated. Upon this fact Wissokowicz bases his explanation of the results obtained by inoculating substances taken from local tuberculosis in man. The reason why, in this instance, rabbits resist while guinea-pigs succumb is, according to this author, not the attenuation of the virus but its dilution; the number of bacilli is too small to overcome the resistance of the rabbits. Dr. Arloing objects to the assertion that a certain number of rabbits or guinea-pigs may become diseased by the injection of diluted bacilli; if, however, the virus is subjected to a temperature of 140° F. (60° C.) for fifteen, thirty, or sixty minutes, it becomes attenuated, and the bacilli are then no longer able to kill the rabbit, though they still render guinea-pigs tuberculous by acting upon these animals like the scrofular virus; the latter virus, therefore, represents an attenuated tubercular virus, a more or less fixed race of Koch's bacillus.

Tuberculosis of Animals. Among the animals most susceptible to the spontaneous development of tuberculosis the bovidæ must first be mentioned. The frequency of bovine tuberculosis varies according to races and countries. While rare in polar countries, tuberculosis is especially prevalent in hot countries, notably in Italy, where it presents the characters of a veritable scourge. Even in those countries in which tuberculosis is most frequent, it is exceptional in young animals; the average for calves is below 1 per 10,000.

The tubercular infection is in some cases expressed by a general malady affecting the serous membranes and resembling human miliary tuberculosis; in other instances, by pulmonary or abdominal lesions; lastly, the bacilli may become localized at a certain point and give rise to local tuberculosis. Pulmonary tuberculosis is undoubtedly the most common form of the disease.

The frequency of mammary tuberculosis has been the subject of much controversy. In less than a year Bang observed seven cases in Copenhagen. In France it seems to be of rare occurrence, and danger of contamination through milk seems to be not so great as was once believed.

Observations upon tuberculosis in the horse are not very numerous. The lesions are sometimes limited to the organs of the abdominal cavity, occupying the viscera and glands; sometimes they are found only in the lungs, and in some instances they are generalized.

Tuberculosis in swine varies according to the countries from 0.1

to 1 per 1000. These estimates, coming from the abattoirs, are probably below the real figures, since the diseased animals grow rapidly thin, and are, therefore clandestinely killed and sold.

Contrary to the assertions of some authorities, tuberculosis in the goat and sheep is not exceptional. Moreover, experimentation proves that the goat can be rendered tubercular the same as other animals.

The remarkable researches of Cadiot[1] have established that tuberculosis is very frequent in the dog. The contrary opinion is due to the fact that, in this animal, the lesions often appear in the form of neoplastic productions, although, in some instances, they are similar to those commonly observed in man—*i. e.*, pulmonary cavities and alterations in the urinary apparatus.

In the cat, as in the dog, tuberculosis may be generalized or limited to the organs of the thorax and abdomen. Voluminous mesenteric adenopathies are commonly present, indicating that the virus has entered through the intestine.

According to the statistics of the London Zoological Gardens, monkeys become tubercular in the proportion of 15 per cent. The infection invades particularly the lungs and the liver, subsequently involving the kidneys, the spleen, and less frequently the intestine.

Contrary to what was formerly believed, rabbits and guinea-pigs, which are so frequently employed for experimental purposes, are seldom, if ever, spontaneously affected by this disease. The so-called spontaneous tubercles are due to cysticercus, coccidia, or to microbes other than Koch's bacillus.

Tuberculosis of the Gallinæ. Tuberculosis of the gallinæ was identified with that of the mammalia when Koch, Ribbert, Babes, Cornil, and Mégnin demonstrated the presence in them of bacilli presenting the same coloring reactions as the bacillus of the mammalia. Soon afterward Drs. Nocard and Roux cultivated the avian bacillus, and their cultures were employed in all the laboratories of France for experimental purposes. The identity of avian and mammalian tuberculoses was accepted without much controversy, since experimentation demonstrated that avian tuberculosis could be inoculated into rabbits, and several observations seemed to point to the transmissibility of human tuberculosis to birds.

It was not long, however, before negative results were reported:

[1] Cadiot. Tuberculose du chien, Paris, 1892, vol. i.

Straus and Wurtz[1] caused chickens and a cock to swallow human tubercular sputa for from six to twelve months; the animals resisted, and the necropsies demonstrated the complete integrity of their organs. Maffucci also demonstrated that mammalian tuberculosis was not transmitted to the gallinæ; twenty chickens were inoculated subcutaneously, by the stomach, lungs, peritoneum, and veins, and all resisted.

The unity of tuberculosis in the various animal species was thus rendered questionable. This doubt was shared by Koch, who, at the Congress in Berlin, declared he had resumed the study of the question and could no longer completely identify the tuberculosis of birds and of the mammalia. From that moment a series of contributions appeared which clearly demonstrated the differential characters of the two forms of tuberculosis. Mention may be made of the numerous investigations which the author pursued with Drs. Cadiot and Gilbert,[2] those of Straus and Gamaleia,[3] and of Courmont and Dor.[4]

The fundamental fact demonstrated by these experiments is one of general pathology—*i. e.*, that tuberculosis may be transmitted from one species to another, but its evolution is directed by the infected organism itself. It is the eternal question of the seed and soil. The hepatic tubercles of the chicken and of the pheasant, for instance, are not only distinguished from the hepatic tubercules of the mammalia, but they are highly differentiated among themselves, although developing in so closely allied animal species. This fact cannot be too strongly emphasized, since it strikingly shows the pathological particularism of animals and indicates the great error of hastily generalizing conclusions drawn from experiments made upon a single animal species.

Comparison of the Tuberculoses of the Mammalia and the Gallinæ. There are certainly numerous differences between the virus

[1] Straus and Wurtz. Sur la résistance des poules à la tuberculose par ingestion. Congrés pour l'étude de la tuberculose, 1888.

[2] Cadiot, Gilbert, and Roger. Note sur la tuberculose des volailles, Soc. de biologie, Oct. 11, 1890. Note sur l'anatomie pathologique de la tuberculose du foie chez la poule et le faisan, ibid., Oct. 18, 1890. Inoculation aux gallinacés de la tuberculose des mammifères, ibid., July 25, 1891. Inoculabilité de la tuberculose des gallinacés aux mammifères, ibid., Feb. 8, 1896. Unicité des tuberculoses humaine et aviaire, ibid., Feb. 8, 1896. Sur un procédé permettant de transmettre la tuberculose des mammifères aux gallinacés, ibid., Nov. 19, 1898.

[3] Straus and Gamaleia. Recherches expérimentales sur la tuberculose. Arch. de médecine expérimentale, 1891. Straus, La tuberculose et son bacille, Paris, 1895.

[4] Courmont and Dor. Tuberculose aviaire et tuberculose des mammifères. Congrés pour l'étude de la tuberculose, 1891.

of the mammalia and that of gallinæ. The avian bacilli are longer and more granular. They develop more readily in artificial culture media and multiply at once in glycerinated agar-agar, while the bacilli of human tuberculosis cannot vegetate in this medium except after having been several times cultivated in serum. The avian bacillus vegetates at 109.4° F. (43° C.) and resists a temperature of 149° F. (65° C.); the human tubercle bacillus ceases to develop at 105.8° F. (41° C.) and dies at 149° F. (65° C.). An avian culture ten months old is living and can yet be sown; a human culture loses its capacity to vegetate in six months (Maffucci). Avian tuberculosis may be transmitted to chickens; it seldom, if ever, causes generalized tuberculosis in guinea-pigs, and, except in certain rare instances (observation of Richet and Héricourt), it cannot be inoculated into the dog. Human tuberculosis is but exceptionally transmitted to chickens; it almost invariably gives rise to generalized tuberculosis in guinea-pigs, and is easily inoculated into the dog.

Such are the differences existing between the two viruses, and all are of secondary importance, which does not warrant their being considered as two different species. The general features of the two bacilli are the same, and the reactions which they arouse in the living organism are similar. The morphological differences are likewise of a secondary order. Differences no less notable are observed when tubercular bacilli present in various individuals of the same species are compared with each other. It is not rare to find in man some bacilli longer and more granular than others.

Agreement is universal as to the identity of the soluble products, notably tuberculin, whatever their origin may be.

These facts point to the conclusion that the two tubercular bacilli represent two varieties of the same species. There are undoubtedly marked differences between the two varieties, and it is impossible to apply to one the results obtained with the other; hence, in order to avoid confusion, it is always necessary to indicate the virus employed. Nevertheless, in conjunction with distinctive characters of importance, we find a common basis warranting the belief that these two pathogenic agents are derived from the same species: unity of tuberculosis of the mammalia and of gallinæ; such seems to us the conclusion suggested by the ensemble of facts thus far observed, which will now find fresh support in the researches pursued by us upon tuberculosis of psittaci.

Tuberculosis of Psittaci.

Fröhner and his assistant, Eberlein, were the first to draw attention to the frequency of tuberculosis in parrots and to show that the disease commonly involved the skin, mucous membranes, subcutaneous and submucous connective tissue, the articulations, and bones. Of 700 parrots brought to the clinics of the Berlin School, 170 were tubercular—say 25 per cent.

The cases studied by the author with Drs. Cadiot and Gilbert[1] were 27 in number. Of these, 15 were tuberculosis of the skin, 9 of the mucous membranes, 6 both of the skin and mucous membranes. The lesions are in the great majority of cases about the head. (Fig. 7).

Fig. 7.



Tuberculosis of the parrot.

In the majority of our observations the lesions presented such a peculiar appearance that their nature could not be recognized before the employment of bacteriological measures. The cutaneous manifestations differ altogether from those observed in other animals; they may be compared only to certain forms of lupus verrucose. There first occurs a shedding of the plumage; then the skin thickens and becomes verrucous, and vegetations soon appear which become covered with thick crusts. If these be detached a granular tissue is exposed. Ulcerations are not uncommon, and are produced espe-

[1] Cadiot, Gilbert, and Roger. Inoculabilité de la tuberculose des mammifères aux psittacés. Soc. de biologie, December 14, 1895. La tuberculose des perroquets, ses rapports avec la tuberculose humaine. La presse médicale, January 26, 1896.

cially when the diseased parts are exposed to traumatism or repeated friction. In certain instances the lesion occupies the subcutaneous tissue; it is a tumor of fibrous consistency which may attain the size of a cherry. Later on the centre softens and is transformed into a caseous mass.

Finally, there is a very peculiar localization which has given rise to many diagnostic errors. The author refers to the tubercles developing near the claws, which become deformed and crooked absolutely as in the cases described under the name of gout of birds.[1]

Visceral manifestations with or without other lesions may occur —gastroenteritis marked by diarrhea, and pulmonary tuberculosis attended by a troublesome and frequent cough.

As parrots live with man and have hardly any communication with other animals, it is reasonable to assume that their tuberculosis is of human origin. That is precisely what observations prove. In a fair proportion of the cases observed by us the tubercular parrots belonged to emaciated individuals with chronic cough, the nature of the affection proving to be tubercular in certain cases which we submitted to bacteriological examination.

Without dwelling upon the inoculability of tuberculosis of both mammalia and gallinæ into the psittaci, as our experiments fully demonstrated, we may say, in conclusion, that the results obtained with the avian virus are altogether comparable to those furnished with the human virus. The parrot, among birds, behaves as does the rabbit among mammalia. These are two animals equally sensitive to the two varieties of tuberculosis.

Having briefly presented the features of human and avian tuberculosis, we may conclude that the various bacilli encountered in man, mammalia, and birds are no more than varieties of one and the same species. It is necessary to admit two principal varieties: one, designated as human, attacks man, mammalia, and, among the birds, the psittaci; the other, improperly called avian, is observed in the gallinæ and sparrows. Numerous facts demonstrate that it is possible, although difficult, to cause each of these two bacilli to lose its so-called specific properties, which means that these properties are not truly specific, since the term species implies fixed virus, not susceptible to transformation. Therefore, in spite of the differential characters of the two great varieties of tuberculosis, we conclude that the disease is one.

[1] Larcher. Mélanges de pathologie comparée et de tératologie. Paris, 1878, p. 153.

Our view, which is likewise that of Drs. Arloing, Nocard, Courmont, Dor, and others, leads to conclusions of practical importance. Since tuberculosis may develop in man through the agency of the avian bacillus (Kruse), tubercular birds, and notably certain dishes prepared with their viscera, should be excluded as food.

The dangers of contamination are greater when parrots are concerned. In these birds the bacilli acquire extraordinary virulence for certain mammalia, as was demonstrated by our inoculations made into guinea-pigs: human tuberculosis is seldom so active upon these small rodents. The bacilli of the diseased parrot are found in the cutaneous productions, saliva, nasal mucus, and at times in the excrements; they may easily be disseminated. Parrots contaminated by man thus become in their turn a permanent focus of tubercular infection.

Pseudotuberculoses.

The expression pseudotuberculosis is applied to a series of very dissimilar lesions having no other common character than the presence of small tumors, the macroscopic appearance of which resembles that of tubercle: in other words, this group includes all those cases in which the granular lesions are not dependent upon Koch's bacillus. It would be logical to include in the group glanders and certain cases of miliary pyemia. We retain the expression because it is generally employed. It is advisable, however, to render its meaning clear by an epithet specifying the kind of pseudotuberculosis concerned. In fact, of the latter there are numerous varieties, which may be divided into four groups:

Pseudotuberculoses by inanimate substances.
Pseudotuberculoses by animal parasites.
Mycotic pseudotuberculoses.
Bacterial pseudotuberculoses.

Pseudotuberculoses by Inanimate Substances. At the time when experimenters were endeavoring to refute Villemin's doctrine it was asserted that any substance introduced into the veins or peritoneum brings about the production of tubercles. These were said to be obtained by injecting pus, putrefied muscle, tissue fragments, and inorganic substances. All the results seemed to be in harmony, from the researches of Lebert and Wyss down to those of Cohnheim and Fraenkel, who subsequently changed their opinion and recognized the specific nature of tubercles.

A good many causes of error had crept into the experiments. Miliary abscesses, infarctions, granulations produced by inert substances, had all been mistaken for tubercular lesions. These granulations have been well studied by H. Martin,[1] who has described three principal varieties: the powder of cantharides produces nodules composed of embryonal cells; with lycopodium the lesion is characterized by giant cells surrounded by round elements; finally, Cayenne pepper induces the formation of true follicles composed of three zones such as are observed in tuberculosis. Since histology was not capable of differentiating these diverse granulations, resort was to be had to experimentation. Dr. Martin showed the pseudotubercles to be devoid of infectious properties. Their inoculation into another animal produced no lesion, or only a few granulations which were no longer inoculable. On the other hand, true tubercle is inoculable in series, and may be transmitted indefinitely from animal to animal.

Analogous productions have been observed in man. Drs. Cornil and Toupet described a cutaneous tubercle composed of follicles, but which contained no bacilli. Careful examination revealed in the centre of the neoplasm the presence of small fragments of oyster-shells around which the lesion had developed. Hanan's observation is no less interesting. At the necropsy of an individual who died thirteen days after perforation of a round ulcer, Hanan found numerous miliary granulations in the parietal peritoneum and in the adhesions which had formed between the liver, diaphragm, and duodenum. These granulations had the structure of non-caseous tubercles; they contained no bacilli, but hard, stony tissue cells of pears.

Pseudotuberculoses by Animal Parasites. Pseudotuberculoses by animal parasites have but exceptionally been observed in man. These are small, yellow, pale, or greenish tubercles varying from a hempseed to a hazel-nut in size.

Among the principal pseudotuberculoses caused by parasites may be mentioned that of the cat, produced by the *ollulanus tricuspis* (Leuckart); that of the sheep, called also verminous pneumonia and due to the *pseudalius ovis pulmonalis* (Koch), and that of the calf, dependent upon the *strongylus rufescens*. These pseudotuberculoses are histologically characterized by simple agglomerations of embryonal cells, and are, therefore, allied to glanders rather than to tuberculosis. Such is not the case with the verminous tuberculosis

[1] H. Martin. Tuberculose des séreuses et du poumon. Pseudotuberculose expérimentale. Archives de physiologie, 1880.

of the dog, produced by the *strongylus vasorum* and well studied by Dr. Laulanié.[1] This observer showed that the ova of strongylus are arrested in the ramifications of the pulmonary artery and induce cellular proliferation within or around the vessels. In the former instance, at the centre of the neoplasm is found a giant cell containing an ovum or an embryo surrounded by epithelioid or embryonal cells; in the latter case, when the tubercles are formed around the vessel, the artery undergoes aneurysmal dilatation and is surrounded by a zone of giant and epithelioidal cells.

Mycotic Pseudotuberculoses. Plants of a relatively higher organism may cause the development of granulations more or less similar to those of tuberculosis. We shall first cite the *streptothrixæ* or *oöspora*, which constitute a transition between bacteria and fungi. The interest attached to this group is the more considerable, since, as has already been stated, the agent of true tuberculosis, Koch's bacillus, is at the present held to be rather a streptothrix. Moreover, the disease most closely allied to tuberculosis, actinomycosis, is due to a fungus which botanists agree should be classed with the same family.

Among other pathogenic streptothrixæ there is one which is the agent of the disease improperly called farcin of cattle (*farcin du bœuf*); this agent, discovered by Nocard, who considered it a cladothrix, is at present known under the designations *streptothrix oöspora, nocardia farcinosa.*

The aspergillus deserves a more careful study. The *aspergillus glaucus* and *fumigatus* produce in animals granulations with giant cells, at the centre of which is found the parasite. These facts, well studied experimentally by Kaufmann and Lichtheim, were completed by the interesting investigations of Dieulafoy, Chantemesse and Widal, Potain, Gaucher, Sergent, and Rénon. These authors described a peculiar disease observed in men whose work compels them to handle grain or flour contaminated with the spores of the *aspergillus fumigatus.* The disease is ushered in as ordinary tuberculosis, by cough, hemoptysis, and a greenish expectoration. The sufferer loses flesh and presents some fever toward evening. Auscultation reveals bronchitic râles and blowing respiration, and at times signs of pleurisy. In other cases the beginning is announced by bronchitis and an asthma-like dyspnea which grows worse at night.

[1] Laulanié. Sur quelques affections parasitaires du poumon et leur rapport avec la tuberculose. Archives de physiologie, 1884.

When the disease is uncomplicated, recovery is the rule after a series of ameliorations and aggravations lasting from three to eight years. Quite often, however, aspergillosis coexists with true tuberculosis, and the latter is responsible for the graver incidents and fatal termination.

The diagnosis cannot be reached otherwise than by microscopic examination of the sputa and by cultures and inoculations. By employing the fluid of Jaulin cultures may be obtained within forty-eight hours. The intravenous injection of sporulated culture kills pigeons in three or four days, guinea-pigs in four or five days, rabbits in six or eight days.

Bacterial Pseudotuberculoses. The great discovery of Koch seemed to permanently demonstrate the unity of tuberculosis. The fact that Toussaint had, in 1880, described a micrococcus found in a tubercular cow was soon forgotten. Although the author succeeded in cultivating the microbe and reproducing the disease in cats, the results were supposed to be due to error, and no attention was given to them. It was, therefore, with a mingled feeling of surprise and incredulity that, in 1883, the profession received from Malassez and Vignal[1] the description of a tuberculosis due to a parasite other than Koch's bacillus. By inoculating a subcutaneous tubercle, taken from a child dead of meningitis, these experimenters produced a disease transmissible in series and apparently due to colonies of zoögleæ which could be seen at the centre of the tubercular nodules. However, the fact that, in continuing their investigations, these gentlemen noticed the gradual decrease of the zoögleæ in successive passages, brought doubt upon the individuality of the infection. Finally, they were replaced by bacilli identical with Koch's. Had an accidental contamination occurred, as was first believed, or a true transformation, as the researches of Bataillon and Terre tended to show? According to the latter hypothesis, zoögleic tuberculosis would be only a form of true tuberculosis.

Zoögleic tuberculosis was found by various authorities. Castro-Sofia found the zoögleæ in an osseous abscess of the instep. Eberth encountered them in a guinea-pig and a rabbit; Nocard in a chicken; Manfredi induced a zoögleic tuberculosis by introducing into the abdominal cavities of guinea-pigs fragments of cotton through which

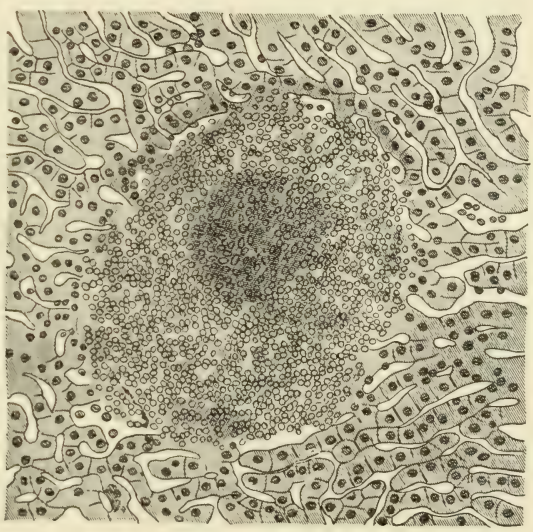
[1] Malassez and Vignal. Tuberculose zoogléique. Archives de physiologie, 1883. Sur le microorganisme de la tuberculose zoogléique. Ibid., 1884.

he had filtered the air of a hospital ward where tubercular patients breathed. Other observations were reported by Grancher, Leroy, Pfeiffer, and others.

The authors who first undertook the study of zoögleic tuberculosis commonly contented themselves with microscopic examinations; the attempts at culture made by them were insufficient to enable them to specify the disease. Having the occasion to observe a pseudo-tuberculosis develop spontaneously in a guinea-pig, viz., without any inoculation, we endeavored to study the disease more thoroughly.[1]

We easily obtained pure cultures of the pathogenic agent and induced the affection in various animal species. Though the lesion

FIG. 8.



Bacillary pseudotuberculosis. Hepatic granulations with central cells strongly stained. × 150.

appeared similar to tubercles when the organs were examined with the unassisted eye, histological examination demonstrated that the granulations differed considerably from true tuberculosis and from zoögleic tuberculosis.

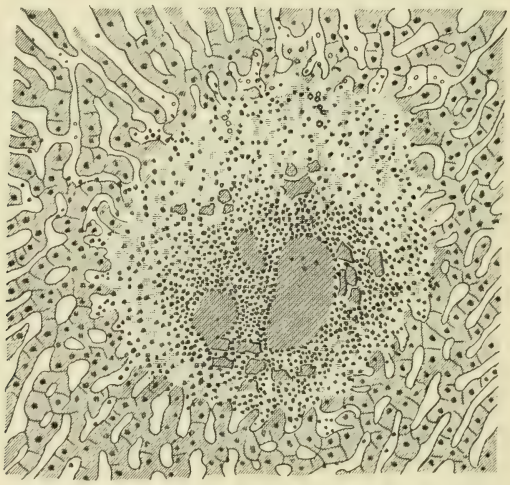
The lesion is of extreme simplicity (Fig. 8); it is a collection of round or epithelioid cells with large nuclei. Nowhere is degeneration observable; the central part is most deeply stained. On the other

[1] Charrin and Roger. Note sur une pseudotuberculose bacillaire. Soc. de biologie and Académie des science, 1888. Roger. Tuberculose et pseudotuberculose. Gazette hebdomadaire, 1890.

hand, in zoögleic tuberculosis the centre of the nodules appears like a granular zone (Fig. 9), and in this zone the parasite accumulates in the form of zoögleæ. In view of the difference in their histological features, we admitted that zoögleic tuberculosis and bacillary pseudotuberculosis represent two distinct affections. Such was also the opinion of Dr. Malassez.

More recently, however, zoögleic tuberculosis was again studied by Drs. Grancher and Ledoux-Lebard,[1] Nocard, and Masselin, as well as Zagari; these authors accurately indicated the characters of the cultures and held our disease to be identical with that of Malassez and Vignal. We believe that the histological study invalidates this opinion, and think that these affections are two different diseases, in spite of their many points of resemblance.

Fig. 9.



Zoögleic tuberculosis. Hepatic granulations presenting three zoögleic masses of a caseous aspect and fragments of hepatic trabeculæ. × 100.

Close to these pseudotuberculoses are: the experimental syphilis of Disse and Taguchi, the pseudotuberculosis observed in the guinea-pig by Morat and Doyon, Bonome, and Cipollina; the pseudotuberculosis engendered by the inoculation of substances suspected to be anthrax (Zagari) or the injection of milk (Parietti); the pseudotuberculosis spontaneously appearing in the antelope (Cornil and Toupet), and in the hare (Megnin and Mosny).

[1] Grancher and Ledoux-Lebard. Recherches sur la tuberculose zoogléique. Archives de médecine expérimentale, 1889 and 1890.

Human Pseudotuberculoses. The study of bacterial pseudotuberculoses is rendered highly interesting by the fact that they occur in man, as is proved by the researches of Malassez and Vignal, Castro-Sofia, Babes, and Masselin. Some recent observations tend to show that they are not of uncommon occurrence.

Drs. Du Cazal and Vaillard[1] made a necropsy upon the cadaver of a man who rapidly succumbed to an infection characterized by fever, diarrhea, and abdominal pains. The peritoneum and pancreas were found to be the seat of an eruption of caseous nodules. These lesions contained a large bacillus, which was cultivated and proved to be a facultative anaërobic, liquefying gelatin and imparting to the cultures the odor of ammonia. Its subcutaneous inoculation reproduced the disease in the rabbit, and its intravenous injection gave rise, according to the dose, to granulations or a septicemia. The guinea-pig appeared refractory.

A short time after this publication, Dr. Legrain[2] described a similar bacillus which was associated with Koch's bacillus in the sputa of a consumptive. Then came the investigations of Hayem and Lesage, who, in a case of tuberculosis of the suprarenal capsules, found a bacillus analogous to if not identical with the one characterizing our bacillary pseudotuberculosis. In pursuing the study of this microbe, Lesage learned that it closely resembled the *bacillus coli communis*.

We must likewise refer to those cases of acute miliary tuberculosis in which Koch's bacillus has not been found. Such are the facts reported by Kouskow, Charrin, and J. Courmont. In the two cases published by Courmont the individuals were the offspring of tubercular parents; the inoculation of their pulmonary lesions into guinea-pigs gave rise to a rapid, atypical tuberculosis.

Thus far, cases of pseudotuberculosis have been encountered in man twelve times, ten times in the rabbit and guinea-pig, twice in cattle and sheep, once in the cow, the antelope, the hare, and the chicken. The microbes must be widely distributed in the soil, as is indicated by their frequent occurrence in small rodents—guinea-pigs and particularly in rabbits—in which animals the disease, the mode of entrance of which is sufficiently evidenced by intestinal lesions, at times prevails in the form of an epizoöty.

[1] Du Cazal and Vaillard. Sur une maladie parasitaire de l'homme transmissible au lapin. Annales de l'Institut Pasteur, 1891.

[2] Legrain. Sur une pseudotuberculose produite par un bacille trouve chez un phtisique. Bulletin médical, 1891.

By collecting the observations thus far published we reach the following classification:

Micrococcic tuberculosis of the cow (Toussaint, 1880).
Zoögleic tuberculosis (Malassez and Vignal, 1883).
Bacillary pseudotuberculosis (Charrin and Roger, 1888).
Pseudotuberculosis (probably zoögleic)
of the guinea-pig (Zagari, Bonome, Cipellina).
of the rabbit (Dor: streptobacillary).
of the hare (Mégnin and Mosny).
of the antelope (Cornil and Toupet).
Fetid bacillary pseudotuberculosis (Parietti).
Pseudotuberculosis of the mouse (Kutscher, Galli-Valério).
Bacillary pseudotuberculosis of the sheep (Preisz and Guinard).
Bacillary pseudotuberculosis of the hog (Galli-Valério).
Human bacillary pseudotuberculosis
of Du Cazal and Vaillard.
of Hayem and Lesage.
of J. Courmont.
of P. Courmont.

Oidiomycosis or Endomycosis.

We have repeatedly stated that infectious diseases are characterized by their clinical evolution and not by the nature of the causative agent. This conception led us to class with infections certain processes dependent upon non-bacterial parasites—plants or even protozoa. The study of the experimental disease which is caused by intravenous inoculation of *oidium albicans* will, we believe, corroborate our argument. Its history represents for us the type of a non-bacterial infection.

Biology of the Parasite. It is not necessary here to speak at length of the morphological and biological characters of oidium; their description will be found in all classical treatises.

It is known that the oidium was found in the productions of buccal aphtha by Langenbec in 1839, and later studied by Berg in 1841. After researches by Gruby we must cite the contributions of Robin,[1] who gave the parasite the name oidium albicans, by which it is now generally known. Its nature, characters of vegetation, and pathological action were definitely fixed by the researches of Grawitz, Plaut, Ch. Audry, Roux and Linossier, Grasset, Charrin and Ostrowsky, Tessier, and Noisette.

More recently, Dr. Vuillemin took up the question from a botanical

[1] Robin. Des végétaux qui croissent sur l'homme et les animaux. Thèse de Paris, 1847. Histoire naturelle des végétaux parasites, Paris, 1853.

standpoint.[1] It was formerly believed that the fungus of aphtha was related to the yeasts and that the filamentous forms were of but secondary importance. Vuillemin, on the contrary, thinks that the filaments are characteristic and must be considered in classing the parasite; then, studying the mode of reproduction, he describes clamydospores and endospores. He lays stress upon the presence of a nucleus found both in the globules and in each filamentous segment. On the ground of these important observations Vuillemin declares the fungus of aphtha to be an ascomyces which should be designated as *endomyces albicans*.

The expression oidiomycosis employed by German authorities and by the author should therefore be rejected. When the ideas of Vuillemin are definitely accepted I shall be glad to use the term endomycosis, as Miss Maria Daireuva[2] writing under inspiration of her master, Vuillemin, thinks I should. In a very important work, Concetti[3] classes this fungus with the group of blastomyces; according to this author, it forms a transition between the latter and the hyphomyces and, consequently, the term *oidium albicans* should be preserved.

If a patch of buccal aphtha be examined under the microscope the fungus is found to present two different forms. At times there will be seen beautiful mycelial filaments; at other times, rounded or oval micro-organisms resembling yeasts. These two forms may be associated or isolated. Out of thirty-one examinations made by us the two forms were found together nineteen times. In twelve cases there were only the yeast forms; once, pure mycelium. It is possible, as is asserted by Miss Daireuva, that the filamental forms are never absent. The reason they are not always detected is that they develop in the depth of the cream-like patch in contact with or inside the mucous membrane.

The two forms above indicated are encountered in artificial cultures. The oval form is mostly observed in solid media, the filamentous in liquid media. These also exist in solid media, but are observed then only at the beginning of development (Stocklin) or in the deeper portion of the culture (Vuillemin.)

[1] Vuillemin. Les characteres spécifiques du champignon du muguet. Comptes Rendus de l'Académie des Sciences, October 24, 1898.

[2] Maria Daireuva. Recherches sur le champignon du muguet. Thèse de Paris, 1898.

[3] L. Concetti. Biologie et pathologie du muguet. Archives de médecine des enfants, August, 1900.

Characters of the Cultures. The fungus of aphtha readily develops in the various nutrient media employed in bacteriology. Agar-agar, gelatin, vegetables, potato, carrot, suit it well. In liquid media the colonies soon fall to the bottom and the fluid becomes clear. Urine and saliva are favorable media, while milk constitutes a bad one. Of all media the most favorable are carbohydrates, especially glucose and saccharose. Whatever medium is employed, the oidium gives rise to fermentation of carbohydrates, resulting in the production of alcohol, aldehyde and acetic acid; hence, the agreeable odor exhaled by the cultures.

The isolated fungi appear in the form of oval elements, measuring from 5μ to 7μ in length. Proliferation occurs by lateral or terminal budding. If a bouillon or serum culture be examined, the filamentous forms are seen measuring 3μ to 4μ in breadth and 15μ to 20μ in length, which, in some instances, may exceed 400μ or even 500μ.

It is, therefore, easy to prove the diplomorphism of oidium by employing solid or fluid medium. It may be assumed that the filamentous form which predominates in fluid media is due to the lack of oxygen; unable to vegetate upon the surface of the fluid, where no film is ever formed, the fungus falls to the bottom, and then sends out prolongations toward the aerated surface. When it is cultivated in a very shallow liquid medium the filaments are seen to become shorter.

Other conditions also influence filamentous growth. The yeast form predominates when the plant is placed under eugenesic conditions; when the media are less favorable the filamentous forms prevail.

Although the descriptions given by authors are mainly in harmony, they differ in many details. These differences in opinion are, in great measure, due probably to the fact that aphtha comprises several varieties.

Role of the Oidium in Human Pathology. The fungus of aphtha is pathogenic for man and certain animals. In the colt, calf, sheep, and hen it produces a white stomatitis which often spreads to the esophagus, presenting the same characters as in man.

Oidian stomatitis, also called creamy stomatitis (*stomatite cremeuse*), aphtha, and thrush, is commonly observed in weakened or cachectic individuals, in the course of diseases which profoundly debilitate the system, grave typhoid fever, urinary and tubercular

infections, cancer, diabetes, etc. As Gubler has shown, its development is favored by the acidity of the mucous membrane. The acidity is due to the excessive multiplication of microbes and to fermentations which they produce in the food, particularly in milk. Thus is produced a catarrhal stomatitis which weakens the resistance. The agents of aphtha being spread in the atmosphere (Lebrun, Roux, Valtat), easily develop in the altered buccal mucous membrane. In other instances the parasite is transmitted directly through the nursing bottle or the breast of the nurse who suckles several children. Finally, it may come from the milk, which is often polluted with *oidium lactis*, a plant closely related to the aphtha parasite.

It is true, however, that aphtha does sometimes develop in healthy individuals, in children by no means athrepsic, in non-cachectic aged persons, and at the beginning of certain infections, notably typhoid fever. It is also encountered in the most varied forms of angina. In a total of 31 cases of diphtheritic angina the writer found it twice; of 46 cases of non-diphtheritic angina 1 showed it combined with the streptococcus; of 116 cases of scarlatinal angina 4 presented it.

Dr. de Stocklin's statistics show the presence of the oidium in 5.75 per cent. of diphtheritic cases, and 10.5 per cent. of non-diphtheritic angina.

The rôle of the *oidium albicans* in these various anginas appears to be of slight importance. Such is not the fact, however, when we consider certain observations of oidian angina progressing as acute sore throat. Teissier reported a case of this sort.[1] A woman, twenty-three years of age, was abruptly seized with chills, malaise, headache and fever. The following day she suffered from intense dysphagia. Examination of the throat showed two small white delicate membranous patches upon the palate which adhered slightly to the mucous membrane. The exclusive presence of the *oidium albicans* was observed under the microscope. In this instance, as well as in that reported by Guimbretière,[2] oidian mycosis started and ran its course as an infection; chills, malaise, and fever were the clinical features. No one would hesitate to consider these mani-

[1] Teissier. Angine pseudomembraneuse produite par le champignon du muguet. Arch. de méd. exp., 1895.

[2] Guimbretière. Essai sur l'angine pseudomembraneuse due au muguet. Thèse de Toulouse, 1896.

festations as infections, if, instead of a fungus, a bacterium was detected!

I have observed a certain number of similar cases. Every year a few patients with acute oidian angina are admitted to our wards. In 1899 we had three such cases. It will suffice to mention one of them, a woman, twenty-three years old, who had chills, violent headache, and dysphagia. A physician called in on the following day diagnosed diphtheria and advised her removal to the hospital. Here we found her throat red, the tonsils greatly enlarged, and white creamy patches the size of a pea occupied the soft palate, right pillar, right tonsil and uvula. Our immediate diagnosis was aphtha, and microscopic examination demonstrated the presence of both mycelium and fungus. It required eight days' treatment to bring about recovery.

The oidium may be encountered in other mucous membranes exposed to the air. It may invade the respiratory apparatus, pharynx, esophagus, or the intestinal canal. In the stomach it may penetrate into the glandular cul-de-sacs and ulcerate them. Valleix and Seux noted its presence in the small intestine and cecum. It has been observed in the anus, vulva and, according to Senator and v. Fritsch, even in the mucous membrane of the bladder.

Whatever may be its seat, the lesion created is of a benign character and commonly of slight tenacity. This fungus does not represent, however, a simple epiphyte. Virchow, Wagner, Parrot, and Letulle have seen it penetrate quite deep into the mucous membranes. Examining the cadavers of thirty-eight children who had succumbed to aphtha, Heller found in two cases the presence of the parasites in the bloodvessels; the latter were the seat of thrombosis in six cases. It is, therefore, conceivable that the fungus may be carried by the lymph and blood currents to the various parts of the system. In fact, it has been observed in otitis media (Valentin), abscess of the gums (H. Grasset), submaxillary abscess (Charrin), and suppurating parotiditis (Guido). At the necropsy of a man who died with right hemiplegia, Zenker[1] found the left cerebral hemisphere full of small, round, granular abscesses, containing the parasite. The starting-point was attributed to the thick membranes of aphtha occupying the throat. This is the first observation of the kind.

[1] Zenker. Soor in Gehirnabscessen. Berichte der Gesellschaft f. Natur und Heilkunde, 1861.

In a child who died from a buccal aphtha twelve days after birth Ribbert[1] found both cerebral hemispheres studded with miliary abscesses, containing oidian filaments. G. Guidi[2] has likewise found the oidium in the pus of cerebral abscesses in a girl three years old. Finally, Dr. Monier[3] published the observation of a cerebral oidian abscess expressing itself, during life, by hemiplegia with Jacksonian epilepsy.

The respiratory apparatus may also be invaded in certain cases. The oidium has been found in the pneumonic focus in a four-year-old child, in the lung of a little girl suffering from fetid bronchitis, and in a pulmonary lesion simulating a hydatid cyst of the liver. Guidi observed the parasite in a pulmonary abscess occurring in a child three months old, which perforated a pulmonary artery, and thus caused sudden death by hemorrhage.

In some instances the nature of the disease has been recognized during life. In an observation of Preyhan, the patient[4] suffered from pulmonary disease, with hemorrhagic pleurisy; her expectoration was sanguinolent and exhaled the odor of fresh yeast, and contained clots formed of the fungi of aphtha.

Oidian lesions have been observed in the various segments of the digestive tract, notably in the stomach and intestine. In an observation of Schmorl[5] the parasite invaded the kidneys and there produced miliary abscesses occupying the surface of the organs.

These observations are very interesting, since they demonstrate that oidiomycosis such as is experimentally produced in animals is a possible event in human pathology, and probably of more frequent occurrence than the cases reported seem to indicate.

Experimental Oidian Mycoses. Klemperer[6] is to be credited with having demonstrated that intravenous injection of a culture of the *oidium albicans* induces a fatal disease, characterized by numerous granulations in the kidneys.

[1] Ribbert. Weitere Untersuchungen über das Schiksal pathogener Pilze im organismus. Deutsche med. Wochenschrift, 1885.

[2] Guidi. Ueber Soor, seine Mykologie und Metastasenbildung. Wiener med. Blatt., 1895.

[3] Monier. Considérations sur les mycoses cérébrales et plus particulièrement sur la généralisation du muguet. Gaz. méd. de Nantes, 1897. Pineau. Le muguet infectieux. Thèse de Paris, 1897.

[4] Preyhan. Pneumonomycosis. Berliner klin. Wochenschrift, 1891.

[5] Schmorl. Ein fall von Soormetastase in der Niere. Centralblatt f. Bakteriologie, 1891, Bd. ix.

[6] Klemperer. Ueber die Natur des Soorpilzes. Centralb. f. klin. Medicin, 1885.

Experiments of Roux and Linossier showed the possibility of nervous symptoms in the inoculated animals. My own researches confirm the descriptions of these authors and demonstrate the frequency and variability of the nervous phenomena.

The more numerous experiments of Grasset[1] added some new facts. These investigations show that intravenous injection produces foci not only in the kidneys, but at times also in the peritoneum, liver, intestine, heart, and spleen. The suprarenal capsules are the seat of lesions appreciable only under the microscope.

The first researches which I published on this subject[2] completed our knowledge of the localizations of the oidium, the histological characters of the lesions, exaltation of virulence, and particularly the modifications presented by the serum of vaccinated animals.

After inoculation the animals remain healthy for a day of two; then they begin to emaciate. Death may occur suddenly. It is often preceded by paralytic manifestations which, with certain cultures, are seldom wanting. The morbid phenomena grow worse, and the animal succumbs in a state of general exhaustion after suffering, in some cases, from convulsions. The necropsy reveals granulations disseminated in various parts of the organism.

Histological Study of the Oidian Tubercle. The histological examination must be directed to the kidneys invaded with nodules.[3] In preparations stained with alum-carmine, and picrocarmine, the granulations appear, under slight magnification, in the form of small masses, which are distinguished from the surrounding tissue by their red color; their limits are not absolutely clear and sharp. Rows of cells extend from the granulations and form prolongations which enter the tubules of the kidney. When more highly magnified the nodules are seen to be composed of collections of embryonal cells, the yellowish portions corresponding to degenerated elements fused into a homogeneous mass (Fig. 10).

Vaccination Against the Oidium. Noisette has shown that the fungi of aphtha degenerate when cultivated in the serum of animals previously infected with the mycotic fungus, and a short time after-

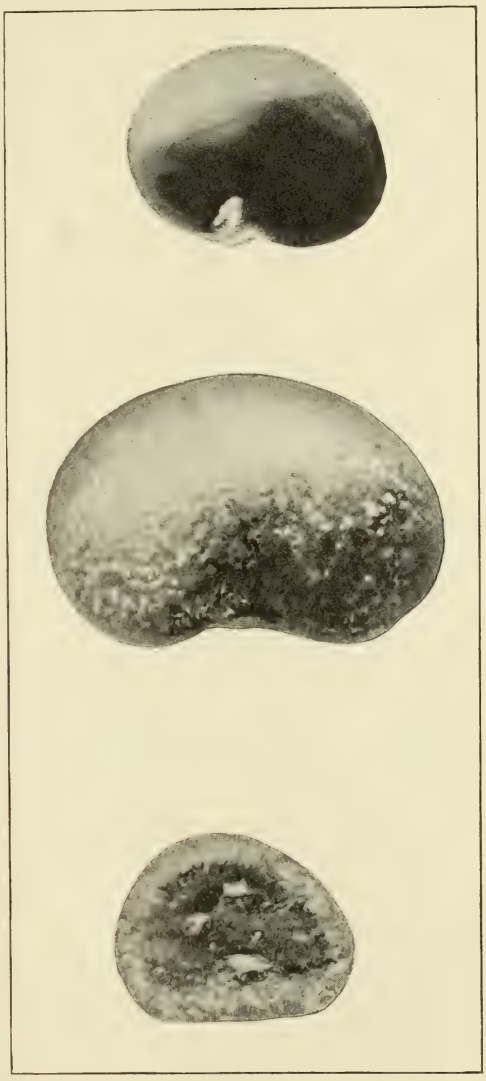
[1] Grasset. Étude d'un champignon pyogène parasite de l'homme. Arch. de méd. exp., Sept., 1893. Étude sur le muguet. Thèse de Paris, 1894.

[2] Roger. Modifications du sérum chez les animaux vaccinés contre l'oidium albicans. Soc. de biologie, July 4, 1896.

[3] Roger and Josue. Des altérations du rein dans l'oïdiomycose experiméntale. Société anatomique, January 2, 1897.

ward they cease to multiply. This reaction was taken advantage of by the author in differentiating the diverse varieties of oidium separated by him.

FIG. 10.



The upper figure represents a normal kidney; the middle one a highly hypertrophied kidney whose surface is covered with oidium granulations; the lower figure represents a transverse section of the diseased kidney (natural size).

The serum of vaccinated animals acts more energetically upon the plant than that of infected ones. In fact, I have learned that

it is possible to confer quite a remarkable degree of immunity upon the rabbit. To succeed in this experiment it is necessary to begin with a weak culture, of which a very small dose is injected into the veins. The doses must be slowly and progressively increased until the animal is able to endure twice or even three times the fatal amount.

The Agglutinating Power of the Serum. Having succeeded in conferring a notable degree of immunity upon the animals, the writer was naturally led to investigate whether the serum of the animals thus treated manifested modifications similar to those observed in animals which had received various bacteria. First studying the serum of animals submitted to subcutaneous and intraperitoneal inoculations, he noticed that aphtha develops in this medium as well as in the normal serum. This result need not be wondered at, since, under these conditions, there has been no increase in resistance. If, however, the serum of rabbits vaccinated by intravenous inoculations be studied, other results are obtained.

Let us take a culture grown in normal serum and inoculate a trace of it into two tubes, one containing normal serum, the other serum of the vaccinated animal. At the end of twenty-four hours development is very luxuriant in the normal serum. In the other serum a few flocculi occupying the bottom of the tube may at times be seen ; at other times no development is apparent, the fluid remains perfectly clear. At the bottom of the tube, however, there is found an accumulation of small granules which manifest a strong tendency to agglutinate so as to sometimes form a single mass. When the fluid is shaken the granules are dispersed, but are not numerous; the culture is a poor one. Increased development is observed on the following days, but the culture remains long or always inferior to that of the control.

The vegetating power of the oidium becomes so weakened in the serum of the vaccinated animal that if, at the end of four or five days, another tube containing the same kind of serum be inoculated with this culture, the fluid remains sterile.

A microscopic examination will suffice to show why the cultures present such different aspects.

At the end of twenty-four hours the normal serum contains (Fig. 11) filaments associated with yeast forms; the latter, at times provided with a terminal or lateral bud, are formed of a mass of protoplasm deeply stained with methylene blue and limited by

a very thin and colorless cuticle. These fungi are free, solitary, or united into groups of twos and threes. Even when thus adhering it is readily seen that each of them has its proper individuality; their cuticles are clearly distinct; there is only juxtaposition, but no fusion with neighboring elements.

The filamentous forms differ from the preceding by the more pronounced development of their cuticles, the small amount of their

FIG. 11.



Appearance of a culture of oidium albicans in *a normal serum.* Beautiful filaments are seen alongside of yeast forms, at times provided with a terminal or lateral bud. The non-homogeneous protoplasm presents dark and light parts; it is limited by a thin and colorless cuticle.

protoplasm, and weaker affinity for the aniline dyes. The filaments are undivided, ramified, or provided with lateral buds having the form of yeasts.

When the culture developed in the serum of the vaccinated animal is examined the appearances are found to be quite different.

Let us first consider a solitary fungus: The protoplasm is colored as in the normal state; it has the same appearance and dimensions.

It is surrounded by a colorless, hyaline, at times a slightly striated mass, with sinuous, illy-defined borders, the length of which is five or six times that of the normal cuticle. The elements are seldom isolated; they form couplets, groups of three, and often groups of voluminous sizes, made up of from ten to thirty elements. It is easy to demonstrate that the condition here is not one of simple juxtaposition, but one of fusion of the cuticles and formation of a true zoöglea. The filaments are here and there intimately united to the fungi, which are either solitary or agglutinated. In other

FIG. 12.



Appearance of a culture of *oidium albicans* in the serum of the vaccinated animal. The elements are united in voluminous agglomerations and surrounded by a colorless hyaline mass. The filaments are likewise composed of a protoplasmic mass surrounded by a very thick cuticle.

instances one extremity of a filament is lost in the midst of a collection of fungi to which it seems to have fused.

Conclusions Concerning the Nature of Oidiomycosis. Oidiomycosis does not differ from bacterial infections any more than the latter do from each other. In fact, it is evidently possible to express in one general formula the mode of action of the various bacteria. When, however, we come to considerations of general pathology, we reach conclusions which, in the majority of instances, are applicable only to certain groups of microbes, but not to all. Oidiomycosis is, therefore, not to be compared to a schematic bacterial infection;

the question is whether it resembles some well-determined infectious disease. By reason of the lesions it produces in animals, the oidium closely resembles the pyogenic microbes, notably the staphylococcus. Indeed, in both cases subcutaneous inoculation is followed by the formation of an abscess. When injected into the veins the staphylococcus, like the fungus of aphtha, gives rise to miliary abscesses. The analogy is continued even in the localization, since the staphylococcic abscesses are often confined to the kidneys; occasionally the cocci invade other organs, notably the myocardium, liver, lungs, and brain. The oidium is equally capable of affecting the same organs in the same manner.

Moreover, vaccination against oidiomycosis is as practicable as in bacterial infections. We have further seen that, in the serum of animals vaccinated against oidiomycosis, modifications similar to those observed in animals vaccinated against bacteria are produced. In both cases the serum becomes bactericidal; it inhibits and weakens the development of the pathogenic agent.

The idea of infection is not established on etiological or pathogenical bases, but on clinical data, to wit, on the reactionary modes of the affected system. The facts above stated demonstrate that the organism acts toward the oidium as it does toward bacteria. Oidiomycosis, then, is rightly classed with infectious diseases.

Pathogenic Role of Yeasts.

The study of oidium is rendered particularly interesting by the fact that this plant represents the best known member of an important group of pathogenic agents. In reality, a great number of yeasts give rise to similar lesions. Thus, Miss L. Rabinowitsch[1] out of fifty species of yeasts taken in Koch's laboratory found seven pathogenic ones. Noisette, employing a certain yeast that is currently on the market, showed that its inoculation produced a mycosis similar to that caused by the *oidium albicans*. San Felice[2] found in the juice of fermented fruits a pathogenic yeast, the *saccharomyces neoformans*.

We may also cite the *saccharomyces lithogens* of San Felice, the *S. niger* of Maffucci and Sirleo, the *S. septicus* of Gaetano, etc.

[1] Lydia Rabinowitsch. Untersuchungen über pathogen Hefearten. Zeitschrift f. Hygiene, 1895, Bd. xxi.

[2] San Felice. Ueber eine für Thiere pathogene Sprosspilzart. Centralblatt f. Bakteriologie, 1895, Bd. xvii.

Here, then, are widely distributed plants, some of them daily employed in the industries, which are capable of engendering diseases.

It may be objected that these are merely experimental results, and that, in order to produce them, such procedures have been resorted to as are never realized in the natural course of events. It is well to know, however, that yeasts are frequently found in the organism. Their presence has been noted in cutaneous ulcers (Babes), in suppurated dental pulps (Miller), in uterine and vaginal discharges (Colpe), in hypertrophied tonsils (de Simoni), in the brains of hydrophobic men and animals (Memmo), and cultures of these parasites have at times produced fatal disturbances in animals.

Recent contributions tend notably to increase the rôle of yeasts in pathogenesis. An interesting observation of chronic pyemia was reported by Busse.[1] The symptoms were due to a saccharomyces the cultures of which induced in animals disturbances similar to those observed in man. There appeared also a series of contributions demonstrating that in man, as well as in certain animals, blastomycetes are frequently encountered in various neoplasms (San Felice, Roncali, Corselli e Prisco, Ajevoli, Secchi, Wlaeff, etc.). It will suffice to mention one among the numerous observations, that of Curtis.[2] It was a case of a myxosarcoma of the thigh, comprising yeast in a state of purity which was successfully inoculated into the connective tissue of a rabbit. This does not mean that yeasts represent the exclusive agents of tumors, but they really seem to give rise to some of them. This is sufficient inducement to draw more attention to their study.

We are thus in the presence of a new chapter, in its formative stage, in the history of infectious diseases. Blastomycetes claim a place alongside bacteria and streptothrix. Oidiomycosis may now be considered as the type of mycotic infections.

Actinomycosis.

Biological Characters of Actinomyces. Actinomycosis is a disease due to the presence of a special plant belonging to the class of streptothrix or oöspora, and occurring in the form of radiate collections visible to the naked eye. They are small, yellow, opaque grains of

[1] Busse. Ueber parasitare Zelleinschlüsse und ihre Züchtung. Centralb. f. Bakteriologie, 1895, Bd. xvi. Ueber saccharomyces hominis. Virchow's Archiv, 1895, Bd. cxl.

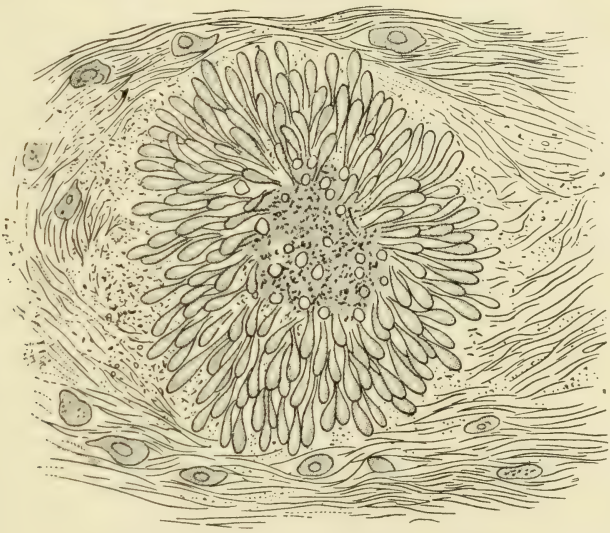
[2] Curtis. Contribution a l'étude de la saccharomycose humaine. Annales de l'Institut Pasteur, 1896.

variable size. Commonly of a golden yellow color, when young they are whitish and translucent; in other instances their color is dark green or sepia.

The grain may easily be crushed. It is formed of small balls measuring from 0.3μ to 0.5μ in breadth and 0.18μ to 0.35μ in length, and when slightly magnified it appears in mulberry form.

Each granulation is composed of a central mass (Fig. 13), whence numerous prolongations radiate, most of which end in a club-shaped enlargement. These enlargements were once considered to be spore-bearing organs, but they simply represent mycelial involution swellings. Their weak vitality explains their frequent infiltration with calcareous salts.

Fig. 13.



Granulation of actinomycosis. × 600.

The actinomyces resist the action of acids, alkali, chloroform, and ether; hot alkalies render them pale and disfigure them; water, even salt water, swells and deforms them.

Cultivation of Actinomyces. Actinomyces has quite often been successfully cultivated in the artificial nutrient media employed in bacteriology. Solidified serum was employed by Irsael.[1] Small nodules composed of grains similar to those observed in the actinomycotic lesions of man and animals made their appearance in the medium on the fourth day. Development is very active on glycerin-

[1] Israel. Ueber die Cultivirbarkeit d. Actinomyces. Virchow's Arch., 1884, Bd. xcv.

ated agar-agar; according to Kischensky,[1] colonies containing rods similar to tubercle bacillus appear as early as the second day; then there appears at each extremity a swelling which stains intensely. Toward the sixth or seventh day the rods become elongated into filaments which, after two or three weeks, bear at their extremities involutive forms which can no longer be stained.

Actinomyces may also be cultivated in liquid media, such as serum, milk, and bouillon. Cultures succeed also upon potatoes and in eggs.

The spores never occur in living organisms. They are encountered only in artificial cultures, to which they impart a notable resisting power.

FIG. 14.



Culture of actinomyces in bouillon, seven months old, after twenty-four hours' incubation. Numerous filaments with club-shaped extremities (*m*), hyaline bulbs (*g*), representing clubs in process of degeneration, and a few spore-bearing filaments (*s*). (Bérard and Nicolas.)

Actinomyces has been variously designated and classed by different authorities. The point conclusively established is that it is not a bacterium, but a fungus, to be placed permanently beside the streptothrix.

Inoculation of Actinomyces. Johne was the first successfully to inoculate actinomyces, by operating upon a heifer and two calves. It has since been possible to produce the disease in the rabbit and guinea-pig, but not invariably. The best results are obtained by

[1] Kischensky. Ueber Actinomycesreinculturen. Arch. f. exp. Path. und Pharmakol, 1889.

the employment of anaërobic cultures or those made in eggs. Liebman[1] thinks the failures are due to the supposed fact that, unlike the great majority of virulent agents, actinomyces is attenuated in passing through the bodies of man and animals; at the same time its vegetability diminishes in notable proportions. It would be possible for the parasite to recover its powers of vegetation and virulence by cultivation in a plant. Various experimenters, however, unsuccessfully repeated the experiments of Liebman.

Etiology. While very frequent among certain animals, especially the bovidæ, actinomycosis is not rare in man. In Bergmann's clinics in Berlin 120 cases were collected in six years. Numerous observations have been reported in France, Switzerland, Holland, and England. In America the first case was observed in 1888 by Bulhoes and Magalhaes. Since that time a great number of cases have been observed in the New World; actinomycosis seems to be of frequent occurrence there, and renders suspicious the meat imported to Europe.

Actinomycosis may be observed in horses, sheep, and hogs, the infection originating from plants upon which these animals are fed. Men are also often affected in the same manner, in handling plants or accidentally swallowing ears of barley, and in many other ways which often remain unrecognized. Alongside the cereals we must place the young shoots of thorny shrubs and the bark of wood altered by moisture and mouldiness.

It is well to mention that the parasite has been found in milk (Bollinger) and eggs (Artant), hence the possibility of contamination by food.

Evolution of Actinomycosis. The anatomical and clinical evolution of actinomycosis is different in man and in animals. In man suppurating foci are encountered; in animals hard tumors, resembling sarcoma. It was once believed that these differences depended upon differences in the parasites. The study of etiology, however, and especially the experiments of Irsael, Bostroem, and Rotter, who transmitted the disease from man to animals, demonstrated the unity of the infection. The peculiar characters of the malady in man are due to the fact that the parasite is associated with common pyogenic microbes which add their action to that of the actinomyces. In certain observations in which actinomyces

[1] Liebman. L'actinomice dell' nomo. Archiv per le sc. med., 1890.

was found to be alone the disease manifested an evolution similar to that observed in animals—*i. e.*, a solid tumor constituted the lesion. Suppuration is not produced in animals, because they are less sensitive to the action of pyogenic agents.

Therefore, in order to form an idea of the lesions created by the parasite when acting alone, actinomycosis should be studied in animals. In the bovidæ the disease is characterized by a voluminous tumor, generally located in the lower jaw and invading the adjacent muscles. In other instances it begins in the periosteum; the bone becomes excavated and filled with morbid matters. The teeth are loosened, and mastication is impossible. If the tongue is invaded, this organ becomes hard (holzzunge (woody-tongue) of German authors) and the animal can no longer use it. The pharynx, respiratory passages, and spine may also be involved.

The disease is seldom generalized, since the animals are killed too soon. Nevertheless, a few cases exist in which the evolution was altogether similar to that of acute miliary tuberculosis. Such for instance, is the very interesting observation made by Pflug upon a cow.

Pathogenic Streptothrix. There exist certain parasites akin to, but not identical with, actinomyces, which are also able to produce lesions.

Aside from *streptothrix farcinosa*, which is not pathogenic for man, we may mention four varieties of streptothrix encountered in the human species: the *S. Fœrsteri*, the *S. asteroides* (Eppinger), the S. of madura foot, and the S. of Poncet and Dor.

Madura foot or *mycetom* is an affection particularly frequent in India, but observed also in America and Algeria. Its invasion is characterized by a painless and diffuse swelling of the integuments of the foot; then appear little tumors which are at first hard, but subsequently soften, break down, and give rise to a sanious pus containing grayish, yellowish, or black granules. The lesion always remains local; there is no propagation by contiguity or by embolism. The affection almost invariably terminates in death.

This parasite is easily cultivated in vegetable infusions and upon potatoes, to which it often imparts a fine red color.

Pseudoactinomycosis of Poncet and Dor is expressed by lesions analogous to those of true actinomycosis,[1] but the yellow grains,

[1] Dor. Une nouvelle mycose à graines jaunes. Gazette hebdomadaire, 1896. Poncet. De l'actinomycose et des mycoses cervico-faciales. Ass. francaise de chirurgie, 1896.

which are less numerous, are much larger and more easily crushed. There are already thirteen observations of this mycosis reported, which seems not to be of very rare occurrence.

Mycoses in Man. Besides the streptothrix there are plants capable of producing lesions more or less similar to those of actinomycosis. The aspergillus and mucors may especially be mentioned.

Paltauf observed a pharyngolaryngeal phlegmon with intestinal ulcerations and pneumonia; in all the foci was found a mucedina similar to the mucor corymbifer of Lichtheim.

A woman expectorated fragments of pulmonary tissue containing masses of aspergillus (Rother). In the case of a young man who was suffering from aspergillian mycosis of the trachea, inhalations of iodine vapor sufficed to cure the affection. Wheaton and Ross published similar observations.

If, in addition to these clinical facts, we bear in mind the experimental results demonstrating that various forms of mucor or of aspergillus may be pathogenic, we are led to the assumption that a good many infections must be dependent upon more highly organized parasites. At the present day we are not thoroughly acquainted with any except actinomycosis, which may, therefore, be regarded as the type of a whole group.

Tumors and Infections.

We do not intend to take up the complex and as yet obscure history of tumors. Although convinced of their parasitic origin, we must frankly acknowledge there are no irrefutable facts to support this opinion. One may take analogies as a basis. It must be recognized, however, that most of the observations upon tumors of parasitic origin thus far reported concern sarcomatous productions. Sarcoma simulates tuberculosis in the dog, actinomycosis in bovidæ, and botryomycosis in the horse. On the other hand, it is undoubtedly true that sarcomata strikingly resemble inflammatory lesions; there is structural analogy, at times identity. The opponents of the parasitic theory would readily yield this group of tumors, but emphatically reject the infectious nature of epithelioma.

There is no doubt that the time is fast approaching when tumors will be differently classified. Lesions of tuberculosis, of glanders, and of syphilis which twenty years ago were still described among the neoplasms by eminent histologists (Virchow, among others)

have already been set aside. The same is true with actinomycotic tumors. Employing the term tumor in its traditional sense, it may be said that there are parasitic tumors. On the other hand, the relations uniting chronic inflammations with adenomata, and these with epitheliomata, seem to prove that reactions caused by the commonest infectious agents may evolve toward the formation of neoplasms. Mechanical irritations of tissues act in the same manner. Traumatism, contusion, and, above all, repeated friction and irritation, may be followed by the development of tumors. The similar rôle of chemical irritation is illustrated by the development of pulmonary sarcoma in men employed in arsenical cobalt factories (Hoerting and Hesse). Finally, larger parasites are also capable of giving rise to tumors. Albarran and Bernard had the opportunity to study a vesical tumor presenting the appearance of epithelioma, which appearance was due, in reality, to the ova of *bilharzia hematobia* present. With Cadiot and Gilbert[1] the writer observed, in an old dog, tumors of the vulva which had deformed the vagina and perforated the wall at several points. Microscopic examination showed that these productions were formed of round cells, in the midst of which acarina were seen.

Experimental Tumors of the Thyroid Gland. The most ordinary inflammations may likewise give rise to neoplastic masses in animals. In this connection we have reported the results of an experiment made in conjunction with Dr. Garnier.[2]

On May 9, 1898, we injected five drops of a diluted culture of the *staphylococcus aureus* into the carotid artery of a rabbit so as to reach the thyroid vessels. Five days later we injected the same amount of the same culture into the other carotid. This rabbit survived three months, until August 11th. It bore on the right side of the neck an irregular but clearly encapsulated tumor as large as a walnut. This hard tumor had the appearance of a sarcoma and contained in its interior softer caseous masses. It represented the right lobe of the thyroid gland extremely developed. The left lobe had preserved its normal form and connections, but looked enlarged.

In microscopic sections of the tumor the thyroideal tissue was

[1] Cadiot, Gilbert, and Roger. Les tumeurs malignes chez les animaux. La presse médicale, July 14, 1894.

[2] Roger and Garnier. Recherches expérimentales sur les infections thyroïdiennes. La presse médicale, August 9, 1900.

completely unrecognizable; nowhere was there any trace of lobule, vesicle, or colloid substance. This tissue was made up of collections of epithelial cells without any orderly arrangement, between which a few connective tissue bands were visible. The epithelial cells appeared to be profoundly modified; the nuclei were very large, vesicular, irregular, and faintly tinged by the ordinary dyes. Large numbers of leucocytes infiltrated the entire tumor; they were often disseminated between the cells; elsewhere they were united in the shape of little islands; their nuclei were small, deeply colored, and contrasted markedly with the light nuclei of the epithelial cells.

The left lobe presented the same structural alteration, but had not undergone the enormous hypertrophy noted in the right one.

It was quite difficult to assign a place in nosology to this morbid production. In reality we were in the presence of a genuine neoplasm, and the great development of the tumor could not be attributed solely to the infiltration by leucocytes. In order to produce this enormous mass the epithelial tissue had abundantly proliferated. It appears, therefore, that the cells had responded to the morbid excitement by increased activity, resulting in considerable multiplication of the epithelial elements and hypergenesis of tissue. Later, all these newly-formed cells degenerated, necrotic foci appeared here and there, and leucocytes wandered in. This, then, was a case of true inflammatory neoplasm in process of degeneration.

Attempts to Inoculate Cancer. If tumors could be successfully inoculated, this would be a powerful argument in support of the parasitic theory. The facts thus far reported are far from demonstrative. Although it seems to be proved that cancer is inoculable from one part to another part of the organism affected, its transmission from a diseased to a healthy individual is doubtful, in spite of a few observations of cancer of the penis in men who had had sexual intercourse with women suffering from uterine cancer. Experimental pathology furnishes no better results; thus far no experimenter has succeeded in transmitting human cancer to animals, nor from animal to animal of similar species. The only positive facts, those of Hanan and of Moreau, concerned rats and mice. According to Menetrier's remark, inoculation is not successful except when practised upon animals of the same family in which cancer has already made its first appearance, and from that moment on it affects several individuals. This is practically equal to the grafting of the disease into the individual itself.

Our own attempts, repeated a great number of times, gave no results. We inoculated the cancer of man into dogs, rabbits, and rats, and the cancer of dog into dogs and rabbits. The inoculations were made beneath the skin, into the peritoneum, and peripheral veins; lastly, in view of the frequency of secondary cancer in the liver, we made inoculations through the portal vein. We constantly failed. We failed even when we endeavored to inoculate into cancerous dogs fragments of their own tumors. In two cases we believed we obtained positive results. In one of them, however, the tumor found in the spleen of an inoculated dog did not present the same histological characters as the mammary neoplasm which had served for the experiment. In the other instance, the lesions presented the macroscopic characters of cancer, but were in reality dependent upon tuberculosis.

These two observations compel us to regard as doubtful the old observations and all those in which no careful study of the histological and bacteriological characters of the lesions were made.

Negative results, however, do not warrant denial of the parasitic nature of tumors. They only suggest modification of experimental methods, since they demonstrate that the problem will not be solved by merely multiplying inoculations according to usual procedures.

CHAPTER XI.

CELLULAR DEGENERATIONS.

Rôle of Toxins in the Development of Cellular Degenerations. Study of the Different Varieties of Degenerations. Cloudy Swelling. Granulo-albuminous Degeneration. Granulo-fatty Degeneration. Fatty Degeneration. Amyloid Degeneration. Pigmentary Degeneration.

The description which has been given of inflammatory phenomena has shown what are the reactions excited at the point attacked by infectious agents. The purpose of these reactions is to circumscribe the lesion and to oppose the diffusion of microbes and toxins. Unfortunately, the barrier is too often inadequate: the microbes and especially the toxins succeed in impregnating the organism and produce various general manifestations.

A local lesion, even when circumscribed, permits the diffusion of substances which impregnate the surrounding tissues. In abscess of the liver, for instance, if the local lesion is intense and of long standing, secondary alterations occur in the hepatic cells; in some cases the cells in immediate contact with the focus are affected; in other instances the whole gland suffers. These secondary changes, however, differ from the lesions produced at the primary focus. The changes observed are not inflammatory alterations, but degenerations.

Although cellular degenerations often predominate in the part primarily attacked, the process may in some cases gradually involve other tissues or organs. A suppuration localized in a bone or joint may thus be complicated with fatty or amyloid degeneration of the principal viscera. An important rôle was once attributed to hyperthermia, insufficient supply of oxygen, respiratory and digestive disorders in the genesis of steatosis. It is at present known that these pathogenic factors are of little importance: the true cause of the morbid events is found in the diffusion of toxins.

The first stage of cellular degeneration consists in *cloudy swelling.* The cells are swollen and filled with an albuminous or serous fluid holding small granules in suspension. The latter present two stages: at first, there is *granulo-albuminous degeneration;* later, *granulo-*

fatty degeneration. In the former case acetic acid swells the granules and then dissolves them; in the latter instance the granules are colored dark by osmic acid. This morbid state is observed in a great number of inflammations; it affects the protoplasm and may involve the nucleus and nucleolus of the cells.

At a more advanced stage we find fatty degeneration, properly so called, or *steatosis.* This process, which plays a notable rôle in pathology, must not be confounded with *fatty infiltration,* which is observed, for instance, in obesity. In the case of fatty infiltration there is simple deposition of fat in the interior of the cell; the protoplasm may be pushed aside, but its activity is not appreciably disturbed. On the other hand, in the case of steatosis or fatty degeneration the protoplasm itself is transformed into fat. Under the influence of nutritional disturbances the proteid substance suffers a peculiar metamorphosis; hence the physiological function of the element is profoundly affected or even completely lost.

Mucoid or *colloid degeneration* is observed in the epithelial cells. It is characterized by the deposition of mucinoid substance in the interior of the protoplasm. This may be compared to *vacuolar degeneration* in which vacuoles appear to be present in the cell. This phenomenon is in reality due to the presence of small cysts filled with an albuminoid substance. In colloid degeneration the material elaborated in the diseased cells may be expelled. If it enters an excretory duct it will be eliminated from the system. Such, for example, is what occurs in the kidney; the colloid masses exuded from the cells unite, coalesce, and form cylinders which are detected in the urine by microscopic examination. When the substance is retained at the point of elaboration it gives rise to the development of more or less voluminous cysts. Thus are explained the cystic degenerations of the kidney and liver, the formation of colloid cysts in the thyroid gland, etc. As the same process, however, may likewise affect pathological cells, cysts may be produced in tumors. The ovarian cyst, for instance, is looked upon as an epithelioma characterized by colloid degeneration.

Another important variety of degeneration is represented by hyaline degeneration. It is essentially characterized by the production of refractive, homogeneous masses. It is frequently encountered in cases of nephritis, in inflammation of the ovary, and in tuberculosis; it is not rare in the small aneurisms found in the walls of tubercular cavities.

Parallel with hyaline degeneration may be placed transparent degeneration, observed by Hanot and Gilbert in the livers of persons dead of cholera. The protoplasm of the hepatic cells becomes completely transparent, the nucleus alone persisting.

Lastly, *Zenker's waxy degeneration* is generally considered to be the same as hyaline degeneration. It is an alteration attacking the striated muscles. It was first encountered in typhoid fever, and was subsequently observed in a great number of infections. It may also be experimentally produced by tetanization of the muscles. It is essentially characterized by swelling, hyaline metamorphosis, and fragmentation of the muscular tissue.

There is no accurate knowledge concerning the nature of hyaline degeneration. It has been noticed that the substance infiltrating the cells resists reagents. This fact is one of the reasons why it is compared to another variety of degeneration, viz., *amyloid degeneration.*

Hyaline degeneration must not be confounded with *glassy degeneration.* The latter is essentially characterized by a transformation of the cell, all parts of which lose their histochemical properties. The protoplasm, nucleus, and nucleolus are no longer differentiated. It would seem, therefore, that this process should be identified with *fibroid degeneration* or *coagulation necrosis.* This is a process similar to the one presiding over the coagulation of organic substances containing fibrin.

It is often stated that glassy degeneration is the first stage of *caseous degeneration.* In fact, it seems certain that the cells are attacked by coagulation necrosis before undergoing the transformation or, one might almost say, the special fermentation which ends in their caseation.

There still remains *pigmentary degeneration,* characterized by a transformation of the protoplasm. It should not be confounded with pigmentary infiltration due to a simple accumulation of pigments transported to the cell. The difference here is the same as that between fatty degeneration and fatty infiltration.

A *sclerotic degeneration* is also often spoken of. This is the process which has already been described as a mode of repair, a true cicatrization. Connective tissue develops in order to replace the cells that have degenerated or disappeared. The cicatrized tissue is sometimes infiltrated with calcareous salts; this process is known as *calcareous degeneration.*

Causes of Cellular Degenerations. Although degenerations differ in their anatomical and clinical expression and occur under conditions peculiar to each of them, and also have a dissimilar significance and evolution, the numerous varieties above described are, nevertheless, related by analogous etiological and pathogenic conditions.

Cellular degenerations always express some nutritional disturbance. The latter may depend upon three distinct causes: 1. Deficient supply of materials destined for nutrition; 2, vitiation of the interstitial plasma—*i. e.*, an intoxication disturbing nutritive metabolism; 3, disturbance or suppression of the functions of the cell.

At the head of the first group is naturally placed starvation. It has been demonstrated by a great number of observations and experiments that suppression of alimentation is speedily followed by cellular degeneration, under the form of fatty metamorphosis.

The same results are observed when the blood is altered, either because it no longer brings to the cells a sufficient amount of aliment or because it is not charged with the requisite quantity of oxygen. The former condition is realized when the blood mass is lessened, for example, as the result of profuse hemorrhages; the latter occurs when the blood corpuscles are altered or decreased in number, to wit, when a local or a general anemia exists.

It is stated that accumulation of carbonic acid produces the same effect as inadequate supply of oxygen, and this explains the occurrence of degeneration in cases of venous obliteration or cardiopulmonary insufficiency. In this case, however, the process is rather one of intoxication, and we are thus led to the consideration of our second group.

It is known that a great number of mineral poisons give rise to cellular degenerations. It will suffice to mention arsenic and especially phosphorus.

The same is true of cases of endogenous intoxication. Whether the question be one of noxious products developed under the influence of cellular life, or one of substances formed by bacteria normally or accidentally inhabiting our bodies, the result is the same. Let us assume, for example, the condition to be one of increased gastro-intestinal putrefaction; as a result of the absorption of excessive amounts of toxins formed, a degeneration of the hepatic and renal cells will occur, and this may prove to be the beginning of a cirrhosis or a nephritis. A good many cases of Bright's disease are due to no other origin.

What is done by the toxins of putrefaction is more fully realized by the toxins of pathogenic agents. The numerous varieties of degeneration above described are encountered in the course of infectious diseases—from cloudy swelling to steatosis, coagulation necrosis, and amyloid degeneration.

We have stated that degeneration may be referable to suppression or disorder of cellular activity. An important distinction must be introduced at this point. In cases of simple lack of function atrophy occurs, but not degeneration. The muscles of an individual who remains inactive diminish simply in volume; when, for instance, a limb is placed in an immovable apparatus, it atrophies but does not degenerate. The same is true of glands which remain at rest. On the other hand, degeneration is produced when lack of activity results from functional disturbance. If a muscle or a gland remains at rest because its nutrient vessels are altered or because the nervous cells controlling the functions or the nerves transmitting the impulses are affected, it is not atrophy but degeneration that occurs. Thus, section of a nerve does not act upon the muscle through the immobility resulting therefrom; the phenomena are more complex—the necessary stimulus is suppressed and degeneration seems again to be connected with a trophic disturbance.

Without wishing to even briefly study the different varieties of degenerations, it may be well to give some complementary information concerning those most frequently encountered and which have thus far only been alluded to: fatty degeneration and amyloid degeneration. We shall then present some considerations relative to pigmentary degeneration.

Fatty Degeneration.

Fatty degeneration or steatosis is essentially characterized by a fatty transformation of the nitrogenous substance which enters into the constitution of anatomical elements. As already stated, this should be carefully distinguished from fatty infiltration, which is in reality a *cellular obesity*. In the latter case fat is stored up in the cellular membrane and, in order to make room for it, the protoplasm is slightly pushed aside. There is addition of a new substance, and not metamorphosis of one already existing.

Fatty degeneration may be established at once or follow another variety, such as granular degeneration, cloudy swelling, or albuminous infiltration. Under the microscope, in specimens fixed by means

of osmic acid, fat appears in the form of small, black granules, isolated or united in masses, and particularly profuse around the nucleus. This steatosis is frequent in the liver, kidneys, myocardium, and muscles. It originates under the most varied conditions. Nutritive disturbances caused by high temperatures are considered important etiological factors, and are supposed to explain the frequency of steatosis in infections. It should be remarked, however, that in this instance the problem is a highly complex one, since the alterations may be more easily accounted for by a production of toxins than by thermal elevation. Nevertheless, the latter pathogenic condition may also be taken into account, because fatty degeneration has been induced experimentally in animals whose temperature was raised by prolonged confinement in an oven. The alteration is supposed to be due to a lack of oxidation, since, under the influence of high temperature, the red blood corpuscles take up less oxygen than under normal conditions.

The same explanation may be applied to other etiological conditions. The steatosis manifesting itself in the course of infections and poisonings may be attributed to deficient oxidation.

Finally, steatosis occurs when an organ is rendered inactive in consequence of suppression of nervous excitation, because metabolism does not progress in a normal manner. Nervous influence is indispensable for the regular performance of nutrition. When this influence fails, oxidation diminishes and fatty degeneration is produced. The more active an organ is, the greater are its demands for oxygen; consequently, if the supply of this gas be diminished, degeneration will first affect those parts which manifest the greatest physiological activity. Among the muscles the myocardium is first attacked, then the diaphragm; among the glands, the liver and the kidneys.

It is not superfluous to note that steatosis occurs when there is diminution but not suppression of oxidations. Stricture of an artery gives rise to fatty degeneration; its obliteration, if not partially compensated by collateral circulation, results in necrosis. Suppression of oxidation ends in the death of the cellular elements.

Amyloid Degeneration.

Amyloid degeneration was described by Rokitansky (1842) under the name *lardaceous degeneration*, by Christensen (1844) under the designation *waxy degeneration*. Virchow (1853) gave it the name

it now bears. In 1858 and 1859 Kekule and Schmidt showed that amyloid tissue is not, as might be assumed, an amylaceous substance; it is an albuminoid—*i. e.*, a nitrogenous substance.

In whatever locality it may be found it is recognized by means of certain very simple reactions. Under the influence of the iodo-iodide test it gives a mahogany-red color, which becomes violet-red on addition of sulphuric acid. On contact with methyl-violet it becomes red.

Amyloid substance is perhaps normally met with in certain parts of the organism. It often constitutes an epiphenomenon in the course of the most varied affections, notably of nephritis. In certain cases it may be so widely distributed that amyloidism is the principal phenomenon. Cohnheim has reported cases in which amyloid degeneration invaded the organism without any cause to explain this alteration. Such an event is exceptional. Amyloid degeneration nearly always occurs in the course of infectious diseases that are liable to induce cachectic conditions, such as tuberculosis, syphilis, and multiple suppurations.

Tuberculosis stands at the head of the list. Amyloidism is commonly observed in patients who have pulmonary cavities, extensive lesions of the intestine, articular or osseous suppurations, necrosis, and caries. The foci nearly always communicate with the exterior. Next comes syphilis, particularly inherited syphilis. The spleen is the organ chiefly affected. Suppurations of long standing may also give rise to amyloid degeneration. Sometimes arthropathies or osseous suppurations; at other times visceral abscesses, dilatation of the bronchi, or multiple abscesses of the skin, are the causative factors. Lastly, among the rarer causes, we may cite cancer, especially ulcerated cancer, and malaria.

This etiological multiplicity shows that individuals of all ages may be attacked. Amyloidism, however, is particularly frequent among men and at the middle period of life, viz., between twenty and thirty years.

Animals are not exempt from this degeneration. As in man, it is encountered in tuberculosis and chronic suppurations. Krawkow succeeded in producing it experimentally. It is constantly observed in tubercular pheasants, in the livers of which the tubercles are surrounded by a zone of connective tissue infiltrated with amyloid substance.

It is at present universally agreed that amyloid matter should be

classed as of nitrogenous origin, but the mechanism presiding over its formation is as yet unknown. Wagner holds this substance to be intermediate between albumins and fats, and this would explain the frequent coexistence of amyloid and fatty degenerations. Recklinghausen believes a homogeneous matter is exuded from the cells which coagulates on contact with the interstitial fluids. In the opinion of Ziegler, the diseased cells are unable to utilize the albumins escaping from the vessels; hence the albumins undergo a special metamorphosis.

At all events, it is certain that amyloid degeneration is closely related to fatty degeneration, since it is produced under the same conditions, and must, therefore, be considered as connected with disturbance of albuminous nutrition.

Amyloid degeneration affects the vessels and the connective tissue in a predominant if not an exclusive manner. In the arteries it begins in the inner coat, sparing the endothelium; it is especially marked in the middle coat. It extends to the capillaries, which it transforms into vitreous, homogeneous tubes lined with epithelial cells which remain intact.

When it affects the organs it appears in three different macroscopic forms. The whole or the greater part of the organ is invaded; the tissue becomes homogeneous, semitransparent, and lardaceous. At other times the process is limited to small foci presenting the appearance of sago grains. Finally, the lesions may be minute and recognizable only under the microscope or by transmitted light in thin sections treated with the usual reagents.

The liver, which is the organ most frequently attacked, becomes considerably enlarged; it appears pasty, lardaceous, and almost bloodless. Under the microscope, infiltration of the capillaries, the hepatic artery, more rarely, of the portal vein, is found. As to the changes in the hepatic cells themselves, discussion is still open. Some authors assert that degeneration occurs; others contend that the vitreous masses encountered are not altered cells, but amyloid masses exuded from the vessels.

The localization is analogous in the other organs. In the spleen it is mainly deposited in the Malpighian corpuscles. In the kidneys it is found in the vessels, glomeruli, connective tissue, and the walls of the uriniferous tubules. The epithelial cells are often altered, but never amyloid. We may also mention the amyloid degeneration occurring in the lymphatic glands, in the intestinal mucous mem-

brane, and the heart, where the muscle cells may be involved (Letulle and Nicolle).

When amyloid degeneration is localized it does not give rise to any special disturbances. Thus, in parenchymatous nephritis, in which it is almost constant, it is not expressed by any appreciable manifestation.

When it is extensive it produces a certain number of phenomena which vary according to its predominance in this or that organ. The first indications are paleness of the patient—paleness of the skin and mucous membranes—and loss of strength. Examination of the abdomen reveals considerable hypertrophy of the liver and spleen; diarrhea is of frequent occurrence; the urine is remarkable for its abundance, pale color, and the great amount of albumin which it contains, at least in certain cases.

Though a fatal termination is the rule, recovery is possible. The patient overcomes the cause that has produced the degeneration, and the latter subsides and finally disappears. Cohnheim, who has laid stress upon this evolution, cites the following experiment: Fragments of amyloid tissue when introduced into the peritoneal cavity of an animal are rapidly absorbed. According to him, it must be concluded that absorption of this substance may occur in the human organism. This experience is interesting, since amyloid matter is very resistant. It is not altered when submitted to artificial digestion with pepsin and hydrochloric acid. Indeed, these are the means generally employed for its preparation.

Pigmentary Degeneration.

There are cases of simple pigmentary infiltration and cases of pigmentary degeneration. The cells may be charged with coloring-matters, particularly the leucocytes, which are often loaded with carbon, even under normal conditions. In other cases the cells may be infiltrated with more or less modified blood pigment derived from former hemorrhage. Finally, various black pigments, apparently derived from the blood, may accumulate in certain anatomical elements without disturbing their function. In the case of pigmentary degeneration, on the contrary, cellular alterations are found which account for the disorders observed during life.

Pigmentary degeneration, which is chiefly observed in malaria, is essentially characterized by the accumulation within the cells of an

okra matter (*pigment ocre* of Kelsch and Kiener, *rubigin* of Auscher and Lapique), which has the property of turning black under the action of ammonia sulphydrate, or blue on addition of potassium ferrocyanide and dilute hydrochloric acid. The latter reaction, which is very sensitive, is currently employed in histology. In preparations thus treated it may be seen that the pigment invades the protoplasm, pushes it aside, atrophies the nucleus and causes disappearance of the latter. All organs are not equally liable to attack. As is always the case, the frequency of the lesions is in proportion to functional activity. The liver is the organ most frequently invaded; next come the kidneys, then the myocardium and the pancreas.

CHAPTER XII.

GENERAL REACTIONS—FEVER.

Functional Synergies and Morbid Sympathies. Contiguity of Organs. Vascular Connections. Rôle of Embolism. Rôle of Humoral Modifications. Nervous Connections. Fever. Definition. Thermometry and Calorimetry. Mechanism. Nervous and Toxic Fevers. Significance of Chills and Sweating. Fever is a Reaction of the Organism. Hypothermia Produced by Toxins. Final Hypothermia in Animals. Persistent Hyperthermia in Man. Causes of this Difference. Production of Heat in Fevers by Retention. State of Oxidations. The Thermogenic Power of the Blood. Rôle of the Liver, Kidney, and Lungs in the Production of Fever. Rôle of the Muscles and Nervous System. Therapeutic Deductions. Characters of Fever in Some Infections. Semiological Value of the Thermal Course.

Functional Synergies and Morbid Sympathies.

The various parts of the system are so closely united by synergies that it is impossible for a lesion to remain absolutely local. On superficial examination the disturbances may appear to be confined to a part of the organism; in reality, however, it necessarily gives rise to a great number of modifications in the entire economy. Reactions may be more or less marked, at times even imperceptible; nevertheless they exist.

It is highly interesting to investigate the mechanism through which the lesions of an organ affect the rest of the system.

The connections existing between the various parts of the organism suggest the following classification of the pathogenic processes of a secondary order:

1. Functional synergies.
2. Contiguity of organs.
3. Vascular connections.
4. Nervous connections.

Referring for the general study of secondary pathogenic processes to the article which the author has devoted to this subject,[1] he will consider only their importance in infectious diseases.

Functional Synergies. As the result of physiological researches and clinical observations, parts which were separated by anatomical

[1] Roger. Les processus pathogéniques de deuxième ordre. Traité de pathologie générale, published by Prof. Bouchard, Paris, 1899, vol. iii. p. 483.

study have been united. Thus are formed physiological unities, acting in harmony and working together to insure the same function. For example, the motor cell, the muscle, and the nerve that unites them represent a whole from the functional standpoint. Pathology agrees with physiology by showing that the alteration of one of these parts effectively influences the others. We cannot, however, expand on these facts, since they present nothing peculiar in infections. When alterations of an organ induce lesions in another the process is an autogenous one which acquires no particular character from the acting cause. Thus, destruction of the cells in the anterior horn of the spinal cord results in atrophy of the corresponding muscular fibres. Here is a striking example of morbid sympathy corresponding exactly to a functional synergy. However, whatever the cause that has produced the cellular lesion may be, the muscle will degenerate. Likewise, when lesions of the liver produce consecutive lesions in the kidneys, the process that has acted upon the hepatic gland imparts no particular character to the renal lesion. It is not superfluous to refer to these facts, for they explain a great variety of symptoms occurring in the course or in consequence of infectious diseases.

Contiguity of Organs. It will suffice to recall for a moment the anatomical positions and mutual relations of organs in order to comprehend how lesions developing in one of them may mechanically affect the others. A purulent focus produced in one part compresses the adjacent parts and produces in them various disturbances which may be transitory—*i. e.*, disappear with the lesion which caused them—or may survive it and run an independent course of evolution.

If the compressing organ is the seat of an inflammatory affection, notably a suppurating or gangrenous lesion, it may, in addition to the mechanical influence, exert a specific action. An inflamed tissue often gives rise to paralysis in subjacent parts. Stokes long ago proved this fact as regards the diaphragm in cases of purulent pleurisy. Likewise, a phlegmonous angina may cause paralysis of the palate. In certain rare instances an acute pericarditis may produce paralysis of the myocardium. What is produced in the striated muscles is likewise observed in the non-striated; such is the case in gastrointestinal paralysis occurring in peritonitis.

Are these paralytic phenomena due to the special influence of the inflamed tissue, or are they the result of the action of soluble products

secreted by the pathogenic agents? It is at present impossible to answer these questions. They require experimental investigations.

Vascular Connections. By acting upon the heart, disturbing its function, altering its tissues, or by creating valvular lesions, infections produce profound modifications in the blood circulation, and thus give rise to a series of disorders throughout the entire system.

Role of Embolism. It is through the vascular system particularly that infectious foci produce lesions in distant parts. Vessels traversing diseased parts are often obliterated either because microbes penetrate into them or because toxins diffuse and give rise to toxic endarteritis or endophlebitis. The latter hypothesis is supported by the fact that emboli are not necessarily infective; they may act mechanically. It is, therefore, possible to observe fibrinous emboli exuded from an obliterated vein in contact with a purulent focus; in other instances fatty emboli occur, originating from an osteomyelitis.

Besides mechanical emboli, there are animate ones which have a highly important bearing on our subject, since they account for the extension and generalization of a great number of lesions. Let us take, for example, actinomycosis. The primary focus may give rise to secondary, sometimes multiple, lesions, which in some cases are sufficiently numerous to suggest pyemia. The same is true of cases of aphtha; and this result is comprehensible, since Wagner has shown that the oidium sends out prolongations into the vessels of the mucous membrane. In this way is explained the formation of visceral foci, such as have been recorded by Zenker and Ribbert.

It is in generalization of infectious lesions especially, however, that phlebitis and embolism intervene. Since the researches of Cruveilhier and Virchow their rôle in the production of pyemia is well known. After having colonized in a clot, microbes manifest a stronger tendency to disperse and multiply in various organs. In fixing themselves upon the vessels they seem to be aided by solid particles which serve them as vehicles of transportation. The secondary lesions which they thus create are similar to those of the original focus. Such is not always the case, however. When, for instance, pyogenic microbes derived from a purulent lesion make their way into the lung they produce in the latter organ lesions which are secondarily invaded by the bacteria of putrefaction, and thus is formed a gangrenous focus.

Emboli generally follow a route traced in advance and governed by the laws of the circulatory mechanics. There are exceptional cases described under the name retrograding or paradoxical emboli. Paradoxical embolism is explained by the persistence of Botal's foramen (Cohnheim, Litten, Zahn). Retrograde embolism is due to cough and effort which disturb the circulation in the inferior vena cava and cause emboli to retrograde in the hepatic and even renal veins (Recklinghausen).

Lymphatic emboli should not be overlooked, although less important than blood emboli. They account for the spread of microbes, and sometimes, especially in the thorax, they may be of retrograde type. These emboli are interesting because they demonstrate the action of the lymphatic glands in cases of visceral lesions and how they, in their turn, may become the source of new lesions.

The effect of embolism may be immediate or remote. Immediate symptoms are observed in cases of large emboli arrested in the heart or an important vessel. They act mechanically, give rise to numerous and at times very grave and speedily fatal disturbances, due either to vascular modifications or, more frequently, to influences of a reflex order.

The violent dyspnea and sudden death in cases of voluminous pulmonary emboli are due, I believe, to a true inhibitory action aroused by the excitation of the intrapulmonary terminations of the pneumogastric nerve.

There are also small, specific emboli. Toussaint attributed to them an important rôle; he argued that most of the symptoms caused by the anthrax bacillus are due to embolic obstruction of the capillaries. This view is not acceptable. The study of infections, however, proves that microbes may emigrate through the vessels and become fixed at a certain point. When arrested the pathogenic agent gives rise to no immediate manifestation; secondary lesions, however, which result in the formation of a new focus are produced around it. Although the process is designated as microbic embolism, there is no true embolus: the microbes are arrested in a vessel because its walls are altered, and the circulation is consequently slow. Thus, a selective colonization takes place without the sudden and abrupt arrest which characterizes true embolism. Logically, the term infectious embolus should be employed when a vessel is suddenly obstructed by a solid particle and notably by a fragment of a clot or valve impregnated with microbes.

Role of Modifications in the Organic Fluids. The vascular system may further serve in the development of secondary pathological processes by distributing throughout the organism soluble products or microbic toxins engendered at a certain point. It is, however, likewise owing to these vascular connections that the toxins are brought to the organs capable of transforming or eliminating them. It is important to note that the increased work thus imposed upon the glandular cells may give rise to new lesions which, in their turn, become the source of other morbid processes.

Nervous Connections. In the presence of the facts thus far considered there can be no escape from the conviction that no lesion can remain local. We have not, however, yet taken into account the highly important rôle of the nervous system, which constantly intervenes to establish solidarity among the various parts of the organism. In the course of a disease the nervous system regulates the formation of inflammatory foci, produces vascular dilatation or constriction, and stimulates or arrests liquid exudations and migration. It also plays an important part in the development of certain symptoms. Let us take cough, for example. In some respects this is a rather favorable disturbance, since its effect is to rid the respiratory apparatus of secretions obstructing the passages. These secretions oppose the penetration of microbes, but their elimination by coughing has the advantage of expelling the pathogenic agents. In order that expectoration may be effected the synergic action of a great number of muscles is required. They are excited to action through reflex influences. The result is the same, however, if the excitant is a poison or some foreign body. The effects resulting from nervous connections possess nothing peculiar in the case of infection. Such is also the case when the microbe or its toxin invades the organism and becomes localized in the nervous system. The functional modifications thus produced acquire no peculiar character from their origin. It is necessary to remark, however, that intoxication of the nervous system may give rise to a great number of functional disturbances. In another chapter we shall see that dyspnea, cardiac disorders, vomiting, and even anuria in many cases depend upon intervention of the nervous system and not upon a lesion of the organs affected. In scarlet fever, for example, early anuria is seldom the clinical expression of a renal lesion; it is due rather to a nervous disorder, and, when the latter ceases, we are surprised to find neither albumin nor casts in the urine.

Fever.

Fever is a morbid state resulting from the exaggeration of the chemical processes concerned in the production of animal heat. These chemical processes may be more active and still retain their normal character, or they may differ from those produced under normal conditions. This distinction is of considerable importance from a therapeutic standpoint, but it does not invalidate the definition above given. Whether deviated from their habitual type or not the chemical acts are more intense; this is the characteristic of fever.

The definition which we propose explains the difference between the terms hyperthermia and fever. *Hyperthermia* (hyperpyrexia) is rise of temperature, whatever the cause. An animal is placed in an oven; its temperature rises 1° or 2°; we then say that this animal presents hyperthermia, but there is no question of fever. Hyperthermia none the less constitutes the principal symptom of fever. Animal heat indicates the measure of the intensity of organic combustion under normal conditions. It, therefore, also indicates the changes which combustion undergoes in pathological conditions. It is intelligible, however, that the results may be modified by increased radiation of heat. For the sake of argument it may be assumed that increase in the production of heat is exactly counterbalanced by increased radiation. The temperature then undergoes no modification. Moreover, if radiation becomes more active it may overbalance the production and, notwithstanding the exaggeration of the chemical processes, the temperature falls. It is thus conceivable that fever may be attended by hypothermia.

These are only theoretical considerations. In order to appreciate their value it is necessary to complete the indications furnished by the thermometer by means of the calorimeter. The amount of heat lost is thus determined. Knowing, on the other hand, the modifications of the temperature, one may easily calculate the quantity of heat produced. It is precisely this quantity that measures the intensity of the chemical phenomena. Fever may therefore be defined as follows, which repeats in another form the definition the author has given above: *Fever is a morbid process characterized by increased production of animal heat.*

Unfortunately, while thermometry is easy of application in clinical medicine, calorimetry can hardly be employed in current practice, for it necessitates the use of delicate apparatus and disturbs the

patient. According to the results of scientific researches pursued on this matter, however, discord between calorimetry and thermometry is quite rare and, at all events, of short duration. Therefore, examination of the temperature is generally sufficient. Practically, it is more important to know the heat of the body than the radiation of the calorics, for it is against the modifications in plus or in minus of animal heat that the physician has to fight. The thermometer alone furnishes him with the necessary indications.

Classification of Fevers. All infections are not febrile, nor are all fevers infectious.

From the standpoint of pathological physiology, all fevers may be divided into two groups: fevers of nervous origin and fevers due to intoxication.

Fevers of nervous origin may be subdivided into three categories:

First, *algic fevers* resulting from painful excitation. This is best illustrated by the so-called hepatalgic fever observed in hepatic colics, even when no symptom suggests infection of the biliary passages. This fever has been experimentally produced in the dog by means of excitation of the biliary passages.

The fevers constituting our second group represent a reaction of the organism aroused by hypothermic action. If an animal be placed in a refrigerator, especially if care be taken to immobilize it, its temperature falls. If the animal then be released and placed in a warm locality, the temperature rises and exceeds the normal. The process is surely one of febrile character, for the hyperthermia expresses increased combustion on the part of the animal in order to struggle against the excessive dissipation of heat.

In the same group may be classed reactionary fevers consecutive to toxic hypothermia. For example, an individual has ingested carbolic acid; his temperature falls to 95° F. (35° C.); a few hours later, however, it rises and reaches 102.2° or 104° F. (39° or 40° C.).

The third variety comprises the febrile movements occasioned by traumatism affecting certain parts of the nervous centres. Their reality has been demonstrated by some observations, notably by a case of meningeal hemorrhage observed in our wards and recorded by Dr. Josue; also by experimental researches, those of J. F. Guyon among others. Hysterical fever may also be classed here.

Fevers of toxic origin are by far the most important. They also include three varieties. At times febrile movement is consecutive to the introduction into the organism of completely formed toxic

substances proceeding from without. The number of hyperthermizing substances is quite restricted. We may cite strychnine and cocaine. At other times fever is due to autointoxication, and, finally, to microbic intoxication.

The reality of fevers due to autointoxication has been demonstrated by numerous experiments and rigorous clinical observations. With this group should be classed the fever of gouty and chlorotic patients, the fever consecutive to the absorption of traumatic sanguineous exudates and to attrition of tissues, certain forms of fever due to overexertion, and the fever of asphyxia.

The fevers of microbic origin evidently constitute the most important group. As has already been stated, however, infections are not always pyrogenic. Chronic diseases, such as syphilis, may evolve without being attended by any elevation of temperature. The behavior of a given infection may altogether differ from one individual to another. Unquestionable observations of apyretic typhoid and scarlet fevers have been published. Apyretic erysipelas is not of uncommon occurrence. Habitually pyrogenic infections, such as pneumonia, are in certain cases attended by subnormal temperature. These well-known facts lead us to the admission that the rôle of the organism is vastly more important than that of the microbe in the production of fever. We shall see that this idea is confirmed by numerous experiments.

It must be recognized, however, that the great majority of acute and even some chronic infections are accompanied by fever and hyperthermia. Are the fever and hyperthermia due to microbic toxins? Experimentation seems to answer affirmatively. The injection of sterilized cultures into animals produces not only hyperthermia, but true fever, with all its modifications in chemical processes. The problem is, however, more complex than appears at first sight. All substances capable of affecting the temperature produce a primary action followed by a secondary reaction of a reverse character. In most cases the latter is not intense; it may, however, especially in infections, be more pronounced than the primary phenomenon and appear so rapidly as to completely mask the primary action.

The questions confronting us, therefore, are: Does fever result from a microbic action? Does it, on the contrary, represent a reaction of the organism against the action of the microbe which tends to produce hypothermia? The latter conception seems to us most in harmony with experimental facts.

Let us first consider the primary element of a great number of febrile processes—*i. e., chills.* At present we know that chills represent a means of getting warm when the body is cold. According to the hypothesis that toxins directly produce fever, it would be necessary to admit that they are capable of directly stimulating the nerve centres concerned in the production of chills. This might be possible, but nothing proves it, and the easier study of ordinary chills reveals no similar fact. It may be objected that chills generally appear when the central temperature has already begun to rise. This result simply proves that the organism began to react against the hypothermizing action of toxins, but that its reaction was insufficient, and for that reason it had recourse to chills, which represent a rapid process of producing heat.

A febrile paroxysm ends by profuse sweating. From the standpoint of thermal regulation, perspiration represents the reverse of chills. It is a means employed by the organism for lowering its temperature. Now, if fever is directly produced by microbic toxins, why does not perspiration appear sooner? This would materially aid the organism to combat the hyperthermizing action of toxins. If, on the contrary, we admit that fever is an expression of a reaction on the part of the organism, it is readily conceivable that it is no longer of any use when the action of toxins ceases. The sweats do not appear from the first, because the organism is struggling against a hypothermizing substance; as soon, however, as the action of the latter ceases, reaction is useless and perspiration begins.

If microbic toxins are hypothermizing, why does the temperature rise above the normal? It would seem that the organism should react only with energy sufficient to keep the bodily heat at its habitual level. In reality, the reactions of the organism are not always measured to the salutary effect. They often exceed the end, and, from this point of view, reaction is, in the present case, too intense. It has not been demonstrated, however, that this exaggeration of the process is useless.

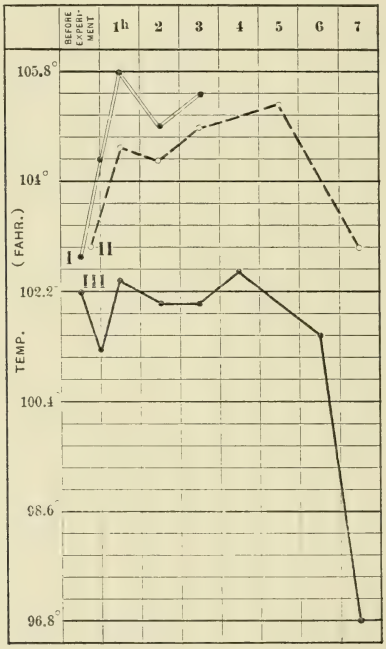
Reasoning thus leads us to the assumption that fever is a reaction of the organism. It will now be seen that experimentation gives considerable support to this theory.

Action of Microbic Toxins upon Temperature. Microbic toxins possess the property of exciting fever when injected in small amounts; when introduced in large doses they lower the temperature. The experiments of Sanarelli with the typhoid toxin, those of Metchnikoff

with the toxin of hog-cholera are, from this point of view, demonstrative. The author obtained a similar result with the toxin of the colon bacillus. This toxin is said to be hypothermizing; in fact, that is what occurs when large doses are injected. When, however, small amounts are introduced, organic reaction takes place and the temperature rises. A glance at Fig. 15 will show that a dose of ten drops produces a thermal rise of 1° or 1.5° C., which persists for five or six hours.

A very small dose, not exceeding half a drop, gives rise to a more intense, at least more rapid, febrile movement. On the other hand,

Fig. 15.



Action of the colon bacillus toxin upon the temperature. I. Injection of 0.025 c.cm. of toxin into a vein. II. Injection of 0.5 c.cm. III. Injection of 18 c.cm.

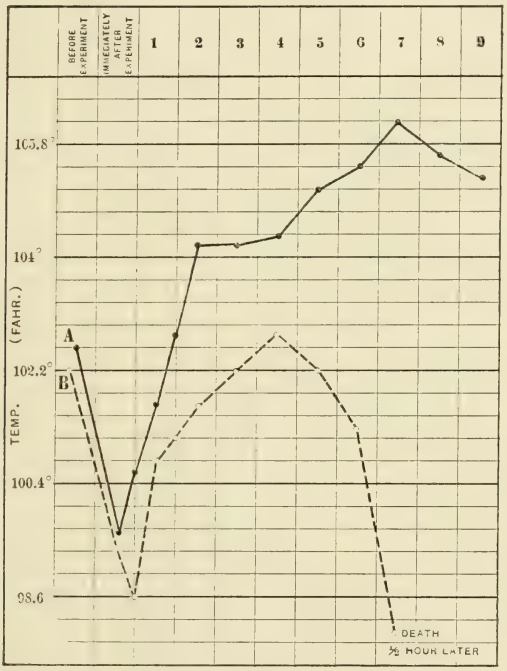
large doses tend to lower the temperature—their first effect is to hypothermize; the organism then reacts, and the temperature rises. It remains close to the normal and then rapidly falls at the moment of death.

The theory which I advocate likewise explains the differences observed in the variations of temperature according to the mode of introduction of the toxin. If a large dose is injected into the veins or the peritoneum, absorption is rapidly effected, and the

temperature falls until the moment of death. If the same amount is deposited in the subcutaneous cellular tissues, absorption being slower, the organism has time to react; the temperature at first rises, to undergo a subsequent fall.

I have found the same differences by introducing the toxin of the colon bacillus by a peripheral vein and by a branch of the portal vein. In the latter instance the poison passes through the liver, which possesses the power of arresting and neutralizing a part of it. Two rabbits of nearly equal weight received each 20 c.cm.

Fig. 16.



Influence of the liver upon febrile reaction. A. Injection of 20 c.cm. of toxin by the portal vein. B. Injection of 20 c.cm. of toxin by a peripheral vein.

of slightly attenuated colon bacillus toxin. In order to render the results comparable, both rabbits were bound for about half an hour to the experiment plank, and the one which received the poison by an auricular vein was subjected to a laparotomy. The two animals were thus placed, with a view to the thermal reactions, under absolutely identical conditions. As soon as the animals were released the temperature in both was found lowered by 1.5° C. From that moment on, however, the temperature rapidly rose in the animal injected by the portal vein (A, Fig. 16), and

exceeded the normal by 2° C. In the other (B, Fig. 16) it first continued to fall, then rose to its initial figure, to again fall rapidly at the moment of death. This animal succumbed at the end of seven hours and a half; the other—the one which received the toxin by a branch of the portal vein—died only at the end of four days.

Similar differences are observed according as the experiment is made upon susceptible or refractory animals. By inoculating anthrax into vaccinated chickens, dogs, or rabbits, fever may be produced; while in animals which succumb to the infection, hyperthermia soon gives way to hypothermia.

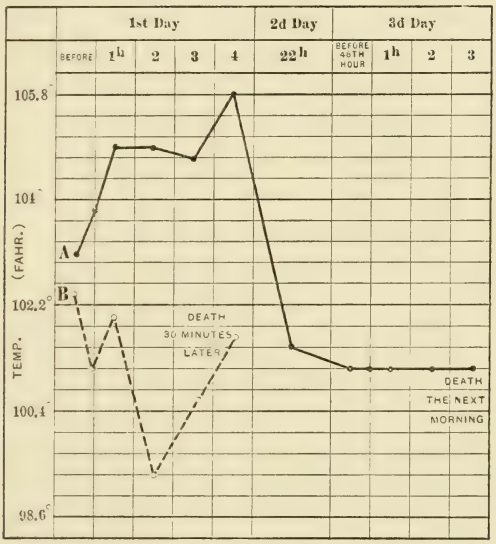
In the same order of ideas may be cited the experiments of Gamaleia, which prove the thermogenic action of cultures to be in inverse ratio to their virulence. Thus, for example, the second vaccine of anthrax bacillus, which kills the rabbit in three days, first produces a rise in temperature, reaching 105.8° F. (41° C.); while an exalted culture which kills the animal in six or eight hours causes no hyperthermia. I have reached a similar conclusion by employing, not living cultures, but toxins. Two cultures of the staphylococcus aureus were prepared, one with a specimen of moderate virulence, the other with the same specimen considerably exalted by means of successive passages. The cultures sterilized by means of chloroform were then injected into two rabbits. One of them (B, Fig. 17) received 5 c.cm. of the toxin obtained from the exalted microbe. It succumbed at the end of four hours and a half in hypothermia. The other (Fig. 17) received 20 c.cm. of the culture made with the attenuated microbes. The temperature rose from 103.2° F. to 105.8° F. (39.5° to 41° C.), and forty-eight hours later the animal was still living. Its temperature then had fallen to 101.1° F. (38.4° C.). Another injection of 20 c.cm. of the same toxin was given. This time the temperature showed no modification. In this organism already exhausted by a first intoxication reaction was no longer possible, and, in fact, the animal was found dead the following morning.

This experiment shows that an animal weakened by a previous injection is no longer capable of developing fever. The result would be absolutely incomprehensible if fever was held to be the result of the action of the toxin; it becomes very clear, however, when it is considered as a reaction of the organism. This experimental fact elucidates certain clinical observations. It explains why cachectic, exhausted individuals develop no fever on the occasion of an infec-

tion. It likewise accounts for the fact that an intercurrent infection supervening in an individual already sick may lower the temperature instead of raising it. This is what occurs, for example, in certain cases of pneumonia developing in the course of a typhoid fever. The organism, already saturated with the typhoid toxin, is unable to struggle against the effects of a new toxin; therefore, instead of rising, as in a healthy individual, the temperature falls.

By another series of experimental infections we observed that the general state of the animals remains quite satisfactory as long as fever lasts, and that aggravation of the symptoms coincides with the fall of temperature.

FIG. 17.



Action of staphylococcic toxin upon temperature. A. Intravenous injection of 20 c.cm. of a moderately active toxin; a similar injection on the third day. B. Intravenous injection of 5 c.cm. of an active toxin.

In man the course of temperature is in general different; in the great majority of acute infections death supervenes in the midst of hyperthermal phenomena. Algid collapse is seldom observed at the end of diseases. The reason resides in the fact that man succumbs before having exhausted all his resources; the animal dies when it is absolutely incapable of struggling against infection, when its reactionary power is completely extinct. Such is not the case with man, because his more sensitive nervous system is sooner poisoned. In the animal the subordinate tissues, the organs of secondary importance, succumb almost simultaneously with the

nervous system; at the approach of death general nutrition is hindered, chemical actions are on the decline, and the temperature is falling; the mammalian is thus practically transformed into a cold-blooded animal. When a moribund animal is killed, red blood is found in its veins and right heart. Even the tissues are found modified in the very same manner as in animals artificially subjected to cold. The nervous system of man cannot accommodate itself to the same unfavorable conditions as that of the animal. It dies while the other tissues are still in full activity, and the chemical actions still keep its temperature above the normal level.

In certain instances, however, human infections lower the temperature. Such is the case in cholera and choleriform enteritis. Such is likewise the case in very acute infections, in certain septicemias consecutive to major surgical operations, and the evolution of which resembles that of traumatic shock. Under these conditions the organism is rapidly overwhelmed and incapable of reacting; according to an expression of Weber, the patient dies in chills and fever.

This result is in perfect harmony with the experimental facts above related. It demonstrates that fever is not produced except when the organism is still able to react.

Mechanism of Fever. Let us now inquire as to what this reaction consists in: does it reside in increased production of heat or in the retention thereof? Both hypotheses have their advocates. Certain experiments, notably those of Rosenthal and Maragliano, demonstrate that during the stage of initial rise the radiation of heat diminishes—a fact which is strictly in accord with those above reported. At the beginning of the febrile movement, when the central temperature is already rising, the peripheral is below the normal; it is at that moment that chills are called into play. Then both temperatures rise, but not with the same rapidity, so that the difference between the central and the peripheral temperature may at times amount to 18° F. (10° C.). The dissipation of heat during the stationary period is equal to or greater than the normal. In cases of transitory febrile paroxysms the dilatation of the cutaneous vessels, which augments the radiation of heat, is produced before defervescence. In cases of prolonged fever there is increased radiation throughout the stationary period.

It results from these facts that, even if there is a retention of caloric at the beginning of a febrile movement, it is exaggerated production that characterizes the stationary period. The losses

being greater, the higher temperature must be due to exaggerated production. It is to be noted, however, that the increase in radiation of heat is not proportional to the increase in its production; hence there is partial retention of the heat produced.

It may now be asked whether there is a simple increase of the normal chemical processes or a deviation from the physiological type.

In order to solve this problem, the excrementitious products eliminated by the respiratory or urinary apparatus should be analyzed.

Some authors, studying the gases of respiration, noted an increase in the exchanges. Wertheim, on the other hand, is of a different opinion. Less oxygen is absorbed, and on this point he is supported by Henrijean's investigations. The amount of carbonic acid likewise undergoes a diminution. The contrary result is due, according to Senator, to the fact that the elimination of this gas is more complete as a result of the acceleration of the respiratory movements and diminution of the alkalinity of the blood.

Dr. Robin has reached conclusions which seem to harmonize the dissimilar results above reported. He carefully distinguishes plain inflammatory infectious states from grave typhoid conditions. In the former instance oxidations are at times normal, oftener more active; they are diminished in the latter. This distinction elucidates not only the modifications in the gaseous exchanges, but also the variations observed in the composition of the urine. The urea is increased, often from 50 to 100 per cent. (Unruh, Senator), in acute cases; while in grave typhoidal states and in fevers of long duration the amount decreases; the extractive matters are then found to be augmented. Probably the alterations developing in the cells, notably in those of the liver, prevent the normal elaboration of the products of dissimilation. These are produced in excess, a fact which accounts for the thermal elevation, but are rejected before having undergone their complete evolution. Finally, the disturbances of the respiratory function seem to be the main cause of the excess of uric acid so often observed in the urine of those suffering from fever (Ranke).

Thus fever is due to increased chemical activity, whether or not there be concomitant departure from the normal evolution of matter. Dissipation of heat in fever is more marked than under normal conditions, but excess in production of heat is still more marked, hence the relative retention of caloric and rise in temperature.

Role of the Blood in Thermal Regulation. The first question is whether the blood is pyrogenic in animals suffering from fever. In this investigation the action of normal blood upon the temperature must previously be determined. The writer has pursued a series of very delicate experiments which are yet in part unpublished and which have led him to some definite conclusions concerning this subject.

Blood taken from the carotid artery of a rabbit was injected into the auricular vein of another animal of the same species, care being taken to operate with extreme rapidity, in order to prevent, as far as possible, the modifications which are easily produced in blood outside the vessels. The blood of a dog, taken under the same conditions, was injected in the same manner. The experiment was also made with defibrinated blood.

Two opposite results were obtained. There occurred a slight diminution of temperature when total blood was introduced into a vein, varying from one-tenth to four-tenths of a degree Centigrade. There was a marked rise of temperature when the same blood was injected defibrinated, the hyperthermia thus produced varying from half a degree to one degree Centigrade. Defibrinated blood acts as the extracts of tissues; in some cases, however, the hyperthermia which it causes is preceded by a slight hypothermia. The blood serum acts like defibrinated blood.

Several hypotheses may be advanced to explain these strange differences which are observed according as total or defibrinated blood is injected.

Defibrinated blood is considered by many authors as a fluid incapable of serving for the nutrition of the organism. To inject it into the veins would mean to introduce a toxic substance, and the febrile movement resulting would then be intelligible. Recent experiments of Dastre have demonstrated, however, that defibrinated blood is perfectly adapted for supplying the needs of the economy. An animal may be bled, and its defibrinated blood may again be introduced into its circulation without any serious disturbance.

The marked instability of organic matter may suggest the supposition that blood becomes thermogenic simply because it has been in contact with air or because it has been kept for a while outside the vessels. With a view to verify this hypothesis we received a certain amount of blood in a vase covered with vaseline. As Freund has

shown, under these conditions coagulation is notably retarded. At the end of half an hour the blood, which was perfectly liquid, was injected into the veins; it produced a slight hypothermia like the normal blood.

It may be supposed that the hypothermizing power of total blood is due to the presence of fibrinogenic substance; the latter, becoming insoluble, allows an antagonistic substance to act. This hypothesis is also contradicted by facts. For the production of thermal elevation it suffices to inject a liquid containing some fibrinogenic substance, for example, the fluid of pleurisy or of hydrocele. The serosity of pleurisy acts, then, like the blood serum. It first induces a slight hypothermia, and subsequently raises the temperature. Hayem[1] likewise obtained hyperthermia by injecting hydrocele fluid into the veins of a dog.

What is known of ferments is in favor of the assumption that the thermogenic action is due to the fibrin ferment. Several observers, and notably Prof. Hayem, have conclusively shown that this ferment raises the temperature. Since its amount notably increases in defibrinated blood and in serum, it was natural to attribute to it the thermogenic property of these fluids. When, however, defibrinated blood is heated to 140° F. (60° C.) sufficiently long to destroy the ferments, the thermogenic power of this fluid is by no means abolished. On the other hand, the results obtained by study of the extracts of blood prepared by means of alcohol or dialysis warrant complete denial of the influence of this ferment.

The nature of the substances capable of modifying animal heat remains therefore undetermined. The facts simply warrant the conclusion that total blood is slightly hypothermizing, and that defibrinated blood and serum raise the temperature, and sometimes raise it after having first lowered it.

There exist, however, certain cases in which arterial total blood is thermogenic, for instance, when the animal which furnishes the blood is sick or when it is submitted to the action of cold. It is not even necessary that the central temperature be lowered in order to render the arterial blood thermogenic. Several times animals that had stayed outdoors in cold winter days furnished the blood which raised the temperature of the transfused animals. It suffices to keep the animal in a well-heated room for twenty-four hours to cause the new property to disappear.

[1] Hayem. Du sang, Paris, 1889, p. 239.

Action of venous blood upon the temperature. A series of experiments pursued by us demonstrated that the venous blood, unlike the arterial, generally raises the temperature of the animals into which it is injected. The hyperthermia is variable, since at times it does not amount to more than a few tenths of a degree C., and at other times it may attain 1° C. or more.

As venous blood generally possesses a thermogenic power which is absent from arterial, the question rises whether this power depends upon substances that are found in the extracts of tissues, or whether it is due to bodies which appear in defibrinated blood, serum, or urine. What modifications does the blood undergo by passing through the lungs? Is it a transformation or an exhalation of volatile thermogenic substances that occurs? Such are the questions to be asked at present, the solution of which requires untiring experimental researches.

Since arterial blood differs from venous by the absence of a thermogenic substance, it is rational to suppose that this substance is eliminated by the lungs. This is, in fact, what takes place. The water obtained by the condensation of the expired air when injected in minute doses into the rabbit causes a more or less marked rise in the temperature.

The hypothermizing power of arterial blood depends upon a substance antagonistic to that eliminated by the lungs; this substance likewise exists in venous blood, but it is often masked by the thermogenic substance.

The hypothermizing substance proceeds from the tissues and is eliminated by the kidneys. It is found in the urine, associated with a new thermogenic substance. In fact, intravenous injections of the urine produce an initial fall in the temperature, noted by Prof. Bouchard, and give rise secondarily to a thermal elevation. Surely we are in the presence of two antagonistic substances, for I have succeeded in separating them. When the urine is treated with alcohol the insoluble substances precipitated in the fluid lower the temperature, while the soluble ones raise it.

It is readily conceivable that these substances, concerning the chemical nature of which we have no data and which we know only through their action upon the organism, may normally play a rôle in the regulation of the temperature. Cold, by stimulating the renal secretion, promotes the elimination of the hypothermizing substance and hinders the exhalation of the volatile thermogenic

element. The effect of heat is evidently the reverse of this; it stimulates the elimination of the volatile thermogenic substance, diminishes the secretion by the kidneys, and hinders the elimination of the hypothermizing element.

These data may explain certain pathological facts and notably the hyperthermia produced by asphyxia and the thermal variations in cases of uremia. As we shall see, they elucidate a certain number of features in the study of infectious fevers.

Role of the Liver, Kidneys, and Lungs in Thermogenesis. Febrile movement may be profoundly modified by lesions or disorders of certain organs. As yet the influence of the liver, kidneys, and lungs only is known.

My attention was drawn to the rôle of the liver by observation of two cases of typhoid fever at the end of 1899. The strange course of the temperature could be accounted for only by the far-reaching alterations which the necropsy revealed in the liver. The disturbances were so pronounced, and modified the clinical course of events to such a degree, that the author thought a hepatic type of typhoid fever should be admitted. Setting aside the concomitant symptoms, let us consider only the course of the temperature. The temperature, lowered in both cases, returned to the normal, and fell even below 98.6° F. (37° C.). Coincidently the general phenomena became aggravated, and the patient succumbed at a time when, if the febrile tracing only was taken into consideration, it would have been thought that he was recovering. The autopsy revealed complete degeneration of the liver, with a bloodless, yellow parenchyma. It was hypertrophied and weighed 1930 grams in one case, 2630 in the other (normal weight being 1500 grams). Histological examination and chemical analysis showed that the gland had undergone acute fatty degeneration; the amount of fat, which normally is about 2 per cent., exceeded 9 per cent.

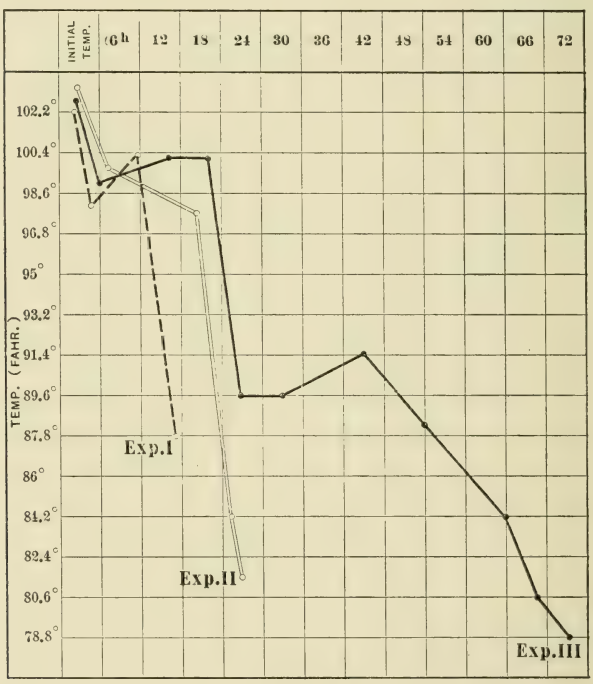
It seemed to me rational to connect the unusual course of the fever with the hepatic alteration. In order to verify this supposition the author undertook some experimental researches. The ideal would evidently be to study the course of the temperature in animals whose liver had been extirpated. Such mutilation, however, is not compatible with a survival sufficiently long to yield demonstrative results. Some other method should therefore be employed. The researches of Denys and Strubbe and those pursued by the author with Dr. Gouget demonstrate that it is possible to destroy the hepatic

cells or, at least, the greater part of them, by injecting a dilute solution of acetic acid into the biliary passages.

The operation is quite simple. A fine canula is introduced through the duodenum into the ductus choledochus in such a manner as not to disturb the course of the bile. The experiment lasts for about half an hour, and the immobilization of the animal and the reflex disturbances resulting from section of the abdomen lower the temperature.

It was therefore necessary to previously study the hypothermia induced by laparotomy. We learned that it generally oscillates

FIG. 18.



Course of temperature in animals in which the liver was extirpated.

about 2.7° F. (1.5° C.) and lasts for a short time; as soon as the animal is released the temperature again rises. If, on the contrary, the hepatic gland is subjected to injury, the temperature, which at times first rises, soon undergoes a new fall in a definite manner, after having often presented slight and transitory rises. Thus, in a rabbit in which 5 c.cm. of a 2 per cent. dilution of acetic acid had been injected into the biliary passages, the temperature, which was primarily at 102.4° F. (39.1° C.), fell after the operation to 99° F.

(37.4° C.); it then rose and two hours later reached 101.1° F. (38.4° C.), but from that moment on it declined; seven hours later it was at 97.9° F. (36.6° C.), and at the end of fifteen hours, thirty minutes before death, it had fallen to 87.8° F. (31° C.).

In another rabbit submitted to the same experiment the temperature followed a similar movement (Exp. I, Fig. 18).

When the animal survives longer the phenomena are more interesting. Thus, in one rabbit (Exp. II.) the temperature fell gradually to 84.2° F. (29° C.) and, a few minutes before death, to 81.5° F. (27.5° C.).

In another instance (Exp. III.) the animal survived seventy-two hours, and the final temperature, a few minutes before death, was 78.8° F. (26° C.).

These absolutely concordant experiments prove that the destruction of the liver is followed by a progressive and very marked lowering of the temperature. The phenomenon is quite difficult of interpretation. Can the liver, according to the experiments of Cl. Bernard, d'Arsonval, and Charrin, be considered as the main source of organic heat? Can it be assumed that destruction of this gland, by suppressing a focus of heat, produces hypothermia in normal subjects and in infected subjects hinders the thermal rise which characterizes fever? This conception might be maintained. It seems, however, more rational to assume that the action of the liver is an indirect one. Suppression of the functions of this organ produces a modification in general metabolism of the economy, a disturbance of the nutritive exchanges which, under normal as well as under diseased conditions, represent the true source of animal heat.

At all events, the explanation is of less importance than the fact. The author's experiments, by demonstrating the existence of a hypothermia of hepatic origin, seem to elucidate some clinical observations. They account for certain disturbances observed in the course of infections affecting especially the liver, notably icterus gravis. Apyrexia and hypothermia are not rare in certain forms of this disease. Is this due, as Hanot asserted, to the nature of the infectious agent concerned? We have experimental evidence that the hypothermizing rôle of the colon bacillus has been exaggerated. Far from lowering the temperature, this microbe often gives rise to fever. The hypothermia of icterus gravis, therefore, seems to be due to hepatic incompetency. It is true that, in certain cases, fever occurs in spite of the hepatic degeneration, because hepatic insufficiency

does not suppress the production of heat any more than renal insufficiency does; it only diminishes it. Moreover, the author has learned by a series of experiments that the injection of microbic toxins into animals the livers of which had previously been destroyed by injecting a 2 per cent. dilution of acetic acid was followed by a thermal elevation which caused the temperature to rise for a moment to its initial height.

The kidneys very likely play a similar part. Incompetency of these organs likewise induces hypothermia, as is evidenced by the course of the temperature in uremic patients. It may, therefore, be supposed that in a certain number of infections fever undergoes oscillations referable to lesions of the kidneys.

On the other hand, pulmonary alterations represent an important cause of hypothermia. Few diseases give rise to such high temperatures as pneumonia. It may be alleged that the phenomenon is due to the action of the pneumococcus; it is, however, the same with bronchopneumonia, regardless of the pathogenic agent, provided, of course, that the sufferer is capable of reacting, for bronchopneumonia in debilitated persons is at times attended by a low temperature which is fairly explained by the general state. On the other hand, that particular clinical form so frequent among children, and which was once described as acute pulmonary congestion, is at present looked upon as an abortive pneumonia and is often accompanied by high fever. Experimentation, by demonstrating that the lungs eliminate thermogenic substances, explains perfectly their rôle in the development of febrile movements.

Except the nervous system, the influence of other parts of the organism is not as yet known. Since the nervous system plays an important part in thermal regulation, it is readily conceivable that according as the nervous centres are excited or paralyzed they may increase or diminish the thermal degree. The intensity of fever in children and its absence in the aged proves this assertion.

To sum up: the fever of infectious diseases is a reaction of the organism against microbic toxins. With the same quantity of the same toxin the febrile movement varies, on the one hand, according to the localization of the process, and, on the other, according to the state of the nervous system, and of the blood, and of certain organs, such as the liver, kidneys, lungs, and, probably, the muscular system, since we know that the principal chemical modifications calculated to maintain the animal heat occur normally in the muscles.

If the author's conception is correct, fever must be considered a struggle against infection. The author speaks of fever, not hyperthermia.

To return to his definition of fever, the author thinks that it is essentially characterized by an exaggeration of the chemical processes occurring in the organism. Whether there be deviation from the normal type or not, there is increase in the phenomena which explain animal heat. In other words, there is increased activity of nutrition. The organism, in order to combat the hypothermizing action of toxins, stimulates combustion, and as soon as a rise in temperature occurs an exaggerated dissipation of heat follows. This fact is interesting, since it is an example—we shall see many others—of a modification which indicates the reappearance of a functional state characteristic of a younger age. It is known that nutrition as well as radiation of heat diminishes with the advance of age; fever, then, is a return to a previous state of the organism.

While fever is useful, hyperthermia may prove dangerous. In combating it, preference should be given to those methods which favor the dissipation of heat, while those that hinder nutritive activity should be avoided. Cold baths offer the best method, since under their influence heat is readily dissipated at an increased rate, and nutrition is at the same time stimulated. This method may, therefore, be considered as a natural one; it is suggested by the procedure utilized by the organism itself.

It is not the elevation of temperature that is to be combated, but an exaggerated elevation of it, since a moderate hyperthermia seems to be favorable to the struggle against the microbes; it stimulates the activity of the leucocytes, as was shown by Dr. Maurel, and it increases the germicidal power of the blood, as has been demonstrated by Kast, Henrijean, and Rovighi.

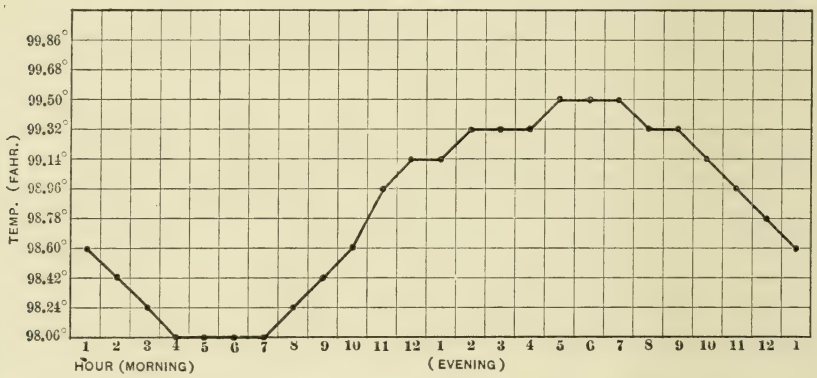
Thus, in spite of a few obscure points, we may at the present day offer a rational conception of fever. In the study of the mechanism presiding over its development we find valuable indications as to its significance, its rôle in the defense of the organism, its usefulness and dangers, and as to the means which, in certain cases, may be employed for restraining and combating it.

Characters of Fever in Some Infections. The application of thermometry to clinical practice has made it possible to learn with precision the characters of fever in various infections. Thus febrile

processes have been divided into four classes, according as they are continuous, remittent, intermittent, or irregular.

The continuous type is represented by cases in which the temperature, at the stationary periods, remains at a determined height. The classical example is typhoid fever. It is necessary to note, however, that the temperature undergoes daily oscillations which are even more pronounced than under normal conditions. It is known that in health the temperature varies at different hours of the day. On awakening, at 6 A.M., it is, on an average, at 98.5° F. (36.9° C.); it progressively rises for sixteen hours, and reaches its maximum, which varies from 99.1° F. to 99.5° F. (37.3° C. to 37.5° C.), toward 7 P.M.; it then declines for eight hours, until 3 or 4 A.M., when it falls to 98.2° F. (36.7° C.), to rise again. It may, therefore, be stated

FIG. 19.



Daily course of the rectal temperature under normal conditions (after Jürgensen).

that, on an average, the normal variation of temperature amounts to 1.4° F. (0.8° C.). The same variations are encountered in disease, but generally they are more marked. In typhoid fever the morning temperature generally varies from 103.1° to 104° F. (39.5° to 40° C.); that of the evening from 104° to 105.8° F. (40° to 41° C.); the difference is 0.9° to 2.7° F. (0.5° to 1.5° C.).

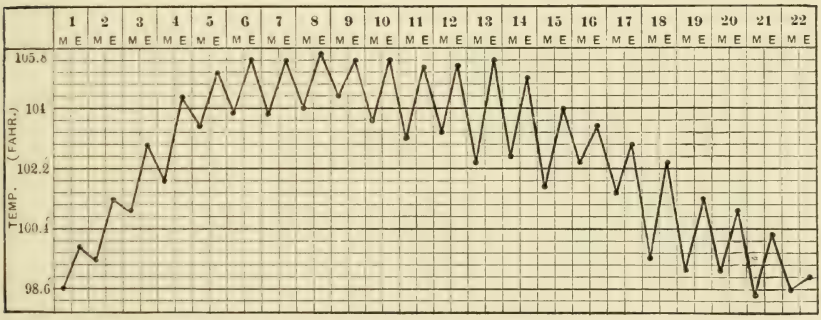
The same is true of pneumonia and typhus, which are likewise characterized at their stationary period by a so-called continuous fever. The digressions are, however, no less clear than in typhoid fever. It may, therefore, be stated that thermal variations in diseases are generally nothing else than exaggeration of normal phenomena.

When thermal remittences are considerable the temperature returns at certain moments to the normal. The fever is then said

to be *intermittent*. Intermittent fevers are often divided into two groups: malarial intermittent and symptomatic intermittent fevers.

The regularity of malarial intermittence is well known. The symptomatic intermittent fevers differ from the malarial in that they are less regular. Unlike what occurs in malaria, fever generally appears in the evening, sometimes recurs several times in one day, and reappears at different hours on the following day. The paroxysms, which in most cases are related to suppurating foci, are connected with the progressively increasing lesions: they are intermittent, while the evolution of the lesions in continuous. They then result probably from a sudden reaction against a cumulative action. Whatever the explanation may be, febrile intermittence is only an exaggeration of physiological remittences.

Fig. 20.



Schematic tracing of temperature of a typhoid case, according to Wunderlich.

In certain infections the course of the temperature is so regular that its study aids diagnosis. Typhoid fever is the type of this kind. Since the works of Wunderlich, the cyclic evolution of the temperature, with its progressive ascension, double summit, and descent by lysis, is well known. (Fig. 20.) To this is contrasted the by no means less typical evolution of pneumonic fever, with its abrupt onset, its plateau, and its defervescence by crisis. The value of these characters should not, however, be exaggerated. Often, especially during grave epidemics, the course of fever in typhoid is absolutely atypical. In order to be convinced of this it will suffice to bear in mind the course of the temperature in the hepatic form of the disease. Even in cases with a typical evolution, however, the course often deviates from the schematic type. At times the onset, at other times the defervescence, is abrupt; in other cases the stationary period is remarkable for

its oscillations, its sudden falls and unforeseen rises. On the other hand, pneumonia may be attended by irregular fever and slow defervescence.

Semiological Value of Thermal Course. As a result of the admirable contributions of Wunderlich it was believed that the determination of the thermal traces would be of great semiological value and furnish important elements in diagnosis. As we have already stated, a different conclusion is at present reached. Medical thermometry serves for differentiating infections only in exceptional instances. It serves rather to inform the physician of the evolution of the process, the development, and at times the imminence of complications, at the same time furnishing him with indications indispensable for treatment. The unexpected rises or falls of the temperature lead him immediately to look for the causes of these unusual modifications. The changes of temperature may thus keep the physician awake to the occurrence of various incidents, such as an intestinal perforation, a hemorrhage, or even a secondary infection; a decrease in fever has on several occasions been observed at a moment when a second pyrogenic infection like pneumonia developed.

Likewise, after an apparent recovery from symptoms, the thermometer may inform us as to a relapse or some incident of convalescence. In other instances it indicates that the food given is too rich or too abundant or that the slight exertion permitted is as yet too fatiguing. Thus, while in the course of disease the thermometer in a large measure guides the treatment, it directs hygienic surveillance during convalescence. In both cases it furnishes valuable indications which no other procedure can.

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CHAPTER XIII.

INFLUENCE OF INFECTIONS UPON VARIOUS PARTS OF THE ORGANISM.

Modifications of the Blood in the Course of Principal Infections. Modifications in the Physical and Chemical Characters. Microscopic Study of the Blood. Variations of the Leucocytes in the Principal Infections. Bacteriological Examination. Modifications in the Hematopoietic Organs. The Bone-marrow. Preliminary Notions of Normal Anatomy and Physiology. Influence of Experimental Infections. Anatomical and Chemical Modifications. Reaction of the Bone-marrow in Man. Semiology of the Bone-marrow. The Spleen in Infections. Modifications in the Lymphatic Glands. Variolar, Syphilitic, and Tubercular Adenopathies. Humoral Modifications of Lymphatic Origin. The Thymus in Infections. The Thyroid Gland in Infections. The Suprarenal Capsules in Infections.

Modifications of the Blood in the Course of Principal Infections.

The diffusion of toxins secreted by pathogenic agents and the intimate solidarity uniting the different parts of the organism sufficiently explain the occurrence of more or less marked modifications in the organs, tissues, and fluids under the influence of infections. These modifications are of two orders: some represent true lesions; others, simple functional changes. Of the latter, some express an increase in activity; at times a return to a previous state—*i. e.*, a kind of rejuvenation of the organism. From this standpoint nothing is more instructive than the study of the blood and of the hematopoietic organs.

Examination of the blood in the course of infectious diseases enables us to watch certain changes occurring in the activity of the organs or in the nutritional processes of the economy, and thus to witness the various phases of the struggle engaged between the invading organism and the invaded. Hematology has this important advantage over pathological anatomy that it is practised upon the living. Post-mortem examination of the viscera shows the results of the defeat, but it does not explain its mechanism. By enabling us to determine at each moment the conditions of the pathological combat, the study of the blood furnishes us with diagnostic and prog-

nostic data of importance, and may even suggest valuable therapeutic ideas.

Modifications in the Physical Characters. Ancient physicians, who frequently resorted to bloodletting, were able to note the organoleptic characters of the blood in the course of infections, and they have left us highly interesting information as to the mode of coagulation and the appearance of clots.

The color of the blood is generally darker than under normal conditions. This excessive venous character is mainly observed when there is a disturbance in hematosis. Gubler and Renaut have noticed however, that in grave typhoid conditions, malignant diphtheria, and hemorrhagic types of eruptive fevers the blood presents a violet hue, different from the dark color observed in asphyxia. They attribute this state to an alteration in the hemoglobin. The same appearance is evidently found at the necropsy. In cholera the blood is remarkable for its thick consistence and dark color. That this is due to some modification in the hemoglobin is demonstrated by the fact that when shaken with oxygen the blood does not resume its red color.

If infection has lasted for a long period and given rise to anemia, the blood is pale and rose-colored. In some grave infections, particularly in nervous forms of typhus and typhoid fevers, it preserves an abnormal arterialization in the veins; it is reddish in color. This may be due to the excessive acceleration of the movements of the heart which, at a given time, causes too much blood to pass into the tissues, or it may depend upon insufficiency of organic exchanges, owing to nervous derangement, and expressed in a diminished production of carbonic acid.

The blood commonly preserves its habitual odor. In certain cases of intense gastrointestinal disorders and putrid lesions, however, it may be charged with nauseous gases. Morton reports that in a bad case of fever the fetid character of the blood where it issued from the vein was such as to almost cause the surgeon and his assistants to faint. It is also said that the blood of variola and typhoid patients exhales a fetid odor.

The modifications in the consistence of the blood played, as is known, an important rôle in the pathogenic doctrines of Boerhaave. It seems that the blood is simply thicker as a result of profuse loss of fluids, markedly in cholera. The total mass is said to be then diminished by one kilogram (quart).

The mode of coagulation of the blood has attracted special attention. In some instances the clot is firm, slightly retractile, and covered with a thick, fibrinous layer: this is the blood of phlegmasias, such as is observed in pneumonia, acute articular rheumatism, and certain phlegmons. In other cases the clot is soft, tending to dissolve in the serum: such is the blood in grave fevers, typhus fever, bubonic plague, and typhoid fever.

In plain phlegmasias, notably in pneumonia, the blood coagulates more slowly than under normal conditions. The clot is remarkably small, concentrated, and firm; the deeper layers are red; the outer surface is formed of a yellowish-white layer which is firm and thick. This appearance of the clot is due to the excess of fibrin, the amount of which may rise from 2.5 to 10 per 1000. As is known, fibrin plays an important rôle in the defense of the organism against the pneumococcus, and it is therefore possible to draw some valuable deductions with reference to prognosis. The upper layer is thicker in proportion as the individual is more robust and the inflammation more intense. According to Hourmann and Dechambre, the blood in the aged is seldom covered by the usual upper layer, a fact well in harmony with the lack of defensive reactions at this age. Louis and Grisolle have noted that the upper layer is often absent in fatal cases and seldom lacking in favorable cases of pneumonia. Among the former it is wanting in one-fifth of the cases; among the latter in only one out of eleven instances.[1]

In grave pyrexias, hemorrhagic types of eruptive fevers, typhus fever, bubonic plague, diphtheria, and pneumonia of typhoid form the blood coagulates slowly and incompletely. The clot is soft, non-retractile. The upper surface is plain, not concave, and covered by a slight layer of fibrin. The serum is scanty and the clot has a tendency to dissolve in the serum.

The mechanism of these phenomena has been a subject of discussion. Some authorities have attributed them to modification in the amount of fibrin, and others to a change in coagulability of the latter. However this may be, the amount of fibrin which coagulates varies markedly with the group of infections considered. The following figures, borrowed from the highly interesting investigations of Andral and Gavarret, give a clear idea in this respect. These authors take the normal proportion of fibrin to be 3: 1000.

[1] Grisolle. Traité de la pneumonie. Second edition, 1864, p. 257.

Disease.	Number of Cases.	Number of Venesection.	Average of Fibrin.	Maximum.	Minimum.
Pneumonia	20	57	7.47	10.5	4.0
Acute articular rheumatism	14	41	6.89	10.2	4.1
Acute peritonitis	4	6	6.2	7.2	4.7
Erysipelas	5	8	5.67	7.3	6.2
Scarlatina	2	2	3.3	3.5	3.1
Variola	5	12	2.92	4.4	1.1
Measles	7	9	2.8	3.6	2.4
Typhoid fever	19	43	2.52	3.8	0.9

Spectroscopic examination of the blood may also be of great service for the study of its physical properties, as has been shown by Henocque. The investigations of Henocque and Beaudoin prove that, in typhoid fever, the energy of consumption of the oxygen of the blood by the tissues is in inverse ratio to the elevation of temperature. Fever diminishes the activity of oxidations and exchanges.

Chemical Modifications. The chemical modifications suffered by the blood in the course of infections are extremely profound, as is evidenced by the modifications in the biological properties of this fluid. They are so delicate, however, and bear upon such unstable substances that an exact analysis is a matter of great difficulty. In fact, no well-marked changes are discovered when the usual procedures are employed.

The reaction remains alkaline. In some cases of cholera it has been found to be neutral or slightly acid. The amount of water varies inversely to the globular richness and increases progressively under the influence of repeated bloodletting. As to the amount of fibrin, pneumonia exerts the most marked influence, since in this disease it reaches the proportion of 7.47 per 1000 on an average, 10.5 being the maximum. Even when this disease occurs in individuals already suffering from an affection which diminishes the amount of fibrin, such as purpura and cancer, pneumonia gives rise to an increase of this substance. It is said that albumin is diminished when fibrin increases. According to Becquerel and Rodier, the addition of these two substances gives the normal total weight.

It would be interesting to study the products of disassimilation, notably urea, ammonia, and extractive matters. Urea is increased in the blood mainly when the renal secretion is profoundly disturbed, as is the case in cholera and variola. In cholera as much as 3.6 per 1000 of urea may be found. On the other hand, when the liver is altered the extractive matters accumulate in the blood.

The variations in the amount of glucose must not be overlooked. I have pursued on this subject some experiments upon animals inoculated with anthrax. In operating upon cadavers I thus noticed that the blood contained no glucose. In view, however, of the rapidity with which sugar disappears after death, the experiment was not conclusive. If blood is taken at the moment when the animal succumbs an extremely intense reduction of Fehling's solution is obtained. During the first stage of anthrax, while the general state of the animal is apparently excellent, the blood contains 0.714 to 1 gram of sugar per 1000. This proportion is somewhat below that found in well-nourished normal rabbits, in which it varies from 1.25 to 1.40 grams per 1000.

During the second stage, when the anthrax bacilli pass into the blood and the temperature of the animal is lowered, sugar increases in notable proportions—it reaches the proportion of 2.24 and even 2.976 grams per 1000. This is probably due to diminished consumption of sugar, as seems to be evidenced by the fall in temperature—another proof of the decrease in nutrition activity.

The chemical modifications of the blood explain the modifications of its biological properties, viz., of its action upon the figurate elements. Thus, the globulicidal power increases in pneumonia, typhoid fever, erysipelas, and tuberculosis. In certain experimental infections the serum becomes more germicidal than normal, even when the disease terminates fatally. These questions will again be referred to.

In recent investigations Achard and Clerc endeavored to show the pathological variations produced in the ferments of the blood serum. These authors proved that considerable attenuation of lipase and amylase is a serious symptom and often indicates approaching death. This result is equally true with regard to cachectic conditions and acute or chronic infections, such as pneumonia, typhoid fever, and tuberculosis. Experimental researches pursued in our laboratory by Dr. Clerc demonstrated the development of similar modifications in inoculated animals. These ferments are the evidences of the activity of the organism. Their study may, therefore, be useful for diagnostic purposes.

Microscopic Study of the Blood. Microscopic examination of the blood shows not only the number and characters of the corpuscles, but also reveals the mode of coagulation of the fibrin and, in some measure, its quantity. Hayem has given a perfect description of

the mode of coagulation of the blood in phlegmasias, such as pneumonia, and rheumatism. Coagulation is slightly retarded. This modification coincides with an increase of the leucocytes and the presence of phlegmasic masses formed of "hematoblasts" which a viscous substance unites with red and white blood corpuscles.

In the majority of infections the number of red blood corpuscles and "hematoblasts" is diminished, and this diminution becomes more and more pronounced the longer the disease continues. The red globules are often altered; they contain less hemoglobin than under normal conditions. Hence they are lighter in color, and some appear completely destitute of pigment. This occurs in cases of adynamic typhoid fever, hemorrhagic variola, and typhopneumonia.

These modifications in the red corpuscles explain in part the disturbance occurring in the respiratory exchanges and, secondarily, in general nutrition. In most cases it is quickly repaired. In certain predisposed individuals, however, reparation is incomplete, and infection is followed by a more or less persistent anemia, at times even by chlorosis. This occurs in consequence of the most varied acute diseases as well as in the course of certain chronic maladies, such as tuberculosis, malaria, and syphilis.

Variations of the Leucocytes. Since attention was drawn to the considerable rôle played by the leucocytes in the protection of the organism, great interest has been aroused in the study of the modifications which these cells may undergo. An endeavor was first made to determine their numerical variations. It has recently been recognized, however, that this study is insufficient; the qualitative modifications must be taken into account; that is, the changes occurring in the different varieties of leucocytes must be determined.

It may be broadly stated that in the majority of infections hyperleucocytosis is produced, which is the more marked the more resistant the individual. Under the influence of the same amount of a given virus a vaccinated animal presents a more intense leucocytosis than an animal without such experience. This result is readily conceivable in view of the protective rôle of the white blood corpuscles. In fatal cases the number of the leucocytes diminishes as the morbid symptoms become aggravated.

The number of leucocytes per cubic millimetre being normally from 6000 to 8000, leucocytosis is said to exist when 10,000 are counted. This figure is often exceeded, but it hardly ever rises

above 30,000, and but exceptionally reaches 60,000 or 115,000, as was the case in a pneumonia reported by Loehr. Among infections which most frequently give rise to leucocytosis we may cite pneumonia, suppurations of all kinds, gonorrhea, and glanders. On the other hand, typhoid fever and measles cause but a slight and transitory increase of the leucocytes. Scarlatina is attended by a leucocytosis which persists long after the fall of temperature. In tetanus leucocytosis varies from 15,000 to 20,000. In tuberculosis the figures are from 10,000 to 20,000. When, however, a caseous focus breaks down and purulent expectoration supervenes the number of leucocytes at times reaches 36,000 (Hayem).

It may broadly be stated that leucocytosis begins, progresses, and declines with the disease.

As to the qualitative modifications of the leucocytes, it must first be noted that it is mainly the neutrophilic polynuclears which are increased. In gonorrhea the eosinophiles are said to increase; in whooping-cough the lymphocytes; in variola and varicella the mononuclears.

It is important to determine for each infection the numerical variations undergone by each variety of leucocytes.[1] This has been done by Chantemesse and Rey for erysipelas. In adults who recover, the polynuclears suffer a diminution until recovery is confirmed. The large mononuclears, the number of which does not vary much during the febrile period, increase considerably immediately before or at the beginning of defervescence. The variations of the lymphocytes follow a reverse course, and their increase is a certain sign of a positive cure. The eosinophiles, commonly absent during the febrile period, reappear at the moment of defervescence. In fatal cases hyperleucocytosis always exceeds 12,000 and is characterized by a polynucleosis which reaches or exceeds the proportion of 92 per cent. The persistence or sudden return of polynucleosis in the course of convalescence indicates the imminence of a relapse. Thus, the interest of this study for diagnostic purposes is considerable.

The same study with regard to typhoid fever has been made by Chantemesse, Millet, and Stienon. At the beginning the absolute number of the leucocytes is diminished. The polynuclears, however, are more numerous than normal. They constitute 70 or even 90 per cent. of the total number. The lymphocytes are diminished,

[1] Consult the general review by Josué, "Formule hemoleucocytaire de quelques maladies infectieuses." Gazette des hôpitaux, December 15, 1900.

while the eosinophiles are almost entirely absent. In the second stage the number of leucocytes is always below the normal; the number of the mononuclears, however, and particularly of the lymphocytes, rises, while that of the polynuclears diminishes by sudden falls. During convalescence the polynuclears are not very numerous, while the lymphocytes increase, and the large mononuclears represent 20 to 30 per cent. of the total figure. The increase in the number of the eosinophiles announces that convalescence will supervene within a day or two. The return to the normal is subsequently effected in a slow or progressive manner. Should some inflammatory complication occur it is announced by a sudden increase in the polynuclears.

In this connection typhoid fever may be contrasted with pneumonia, which, unlike the former, is a disease characterized by an abrupt development. Numerous hematological investigations demonstrate that the number of leucocytes rises suddenly after the initial chills. The polynuclears predominate; before the crisis they reach 80 per cent.; on the eve of crisis they rise to 86 per cent., to fall to 71 per cent. after defervescence and to 57 per cent. on the days following (Leredde). At this moment an increase in lymphocytes and eosinophiles is observed, the latter rising from 3 per cent. to 5, to 6, or even 7 per cent. (Türck). In cases in which polynucleosis persists after defervescence the termination of the disease should be considered incomplete. If the polynuclears increase, suppuration of the exudate is to be feared.

The infections characterized by mononucleosis constitute a very particular group. Aside from whooping-cough (Mennier) the pathogenic agent of which is unknown, we see that all of them are produced by protozoa. This has first been demonstrated with regard to malaria. During a paroxysm there is first an increase of lymphocytes and, in a less degree, of eosinophiles and large mononuclears. Fifteen to twenty minutes later the lymphocytes are more numerous and the large mononuclears rarer. The polynuclears undergo scarcely any change.

The author believes variola to be due to a protozoön of a quite different order. Whether this parasite develops in man or is inoculated into rabbits it gives rise to mononucleosis. Leucocytosis may be moderate. In a total of 36 cases, studied in our wards, we found 19 times 6000 to 15,000 leucocytes per cubic millimetre, 12 times 15,000 to 20,000, 3 times 25,000, and in the last two cases 30,000 to

35,000. Although leucocytosis is present from the beginning, it is particularly intense at the time of vesiculation, and remains stationary, slightly diminishes, or increases during pustulation. In the hemorrhagic forms it is less marked, but is seldom absent.

In scarlatina the number of the leucocytes is, according to Kolshetkoff, from 10,000 to 20,000 in light cases, 20,000 to 30,000 in cases of ordinary intensity, more than 30,000 in grave cases. The polynuclears represent 85 to 98 per cent.; the eosinophiles, which are slightly decreased at the beginning of the disease, grow more and more numerous during its course; they diminish and may even disappear in grave cases.

Bacterioscopic Examination of the Blood. Microscopic examination of small drops of blood at times reveals the presence of pathogenic agents, and thus gives valuable clinical information. Such is particularly the case in malaria—the presence of the peculiar hematozoön enables us to reach a positive diagnosis. In hemorrhagic variola, as well as in congenital smallpox, the blood contains corpuscles characteristic of this infection. The same elements are found in the blood of inoculated animals, at least when the disease evolves rapidly.

When practised during a paroxysm of recurrent fever, examination of the blood reveals the presence of the spirilla of Obermeier. The parasite cannot be seen during the intervals of the paroxysms.

The microscope more rarely permits the detection of bacteria. The latter are hardly ever seen except toward the end of diseases. Such particularly is the case in anthrax—the presence of the anthrax bacilli in the blood indicates a general infection and announces the approach of a fatal termination.

This does not mean that bacteria do not invade the blood, even in cases of curable infections, but that the germs are always present in such small numbers that it is difficult to detect them by a simple microscopic examination. To obtain precise information, cultivation and, sometimes with advantage, inoculation must be resorted to. By employment of these various procedures the tubercle bacillus has been detected in the blood in cases of acute miliary tuberculosis (Weichselbaum) and, more rarely, the bacillus of glanders and that of typhoid fever. The latter, which is only very exceptionally encountered in the blood of the general circulation, is often met with in the rose-colored spots of the skin and, almost constantly, in the blood of the spleen.

The microbes of septicemia—the staphylococcus, streptococcus, and pneumococcus—invade the blood oftener than is generally believed, but they are present in such small numbers that it is difficult to detect them. When, however, a considerable amount of the blood is cultivated or inoculated it is seen that the microbes are present in the blood even in benign cases, although they are more numerous in grave cases. In this respect the figures given by Beco are altogether conclusive. Of fifty-six patients suffering from pneumonia eleven had the pneumococcus in the blood. Of twenty-nine of these patients who recovered, in only two was the blood invaded. Among the twenty-seven who died the blood was infected in ninety.

It is well to add that the staphylococcus has also been found in the blood in cases of furunculosis, anthrax, osteomyelitis, and puerperal or surgical infections. According to Sittmann, its presence does not render the prognosis so serious as does that of the streptococcus or pneumococcus.

Modifications of the Hematopoietic Organs. Of the numerous modifications suffered by the blood in the course of infectious diseases some are, perhaps, due to the direct action of microbic toxins, but most of them depend upon previous modifications of the organs or tissues. The blood being a production of cellular origin, its changes indicate previous modifications in the organs concerned in the task of assuring its chemical constitution or furnishing it with figurate elements. It is, therefore, natural to investigate the occurrences in the hematopoietic organs. For consideration of the morphological elements attention must be drawn to the organs in which the red and the white blood corpuscles are formed—the bone-marrow, spleen, lymphatic glands, and the thymus.

As a result of the admirable researches of Ehrlich it was believed that the hematopoietic organs could be divided into two groups. One group is constituted by the lymphoid tissue and gives rise to non-granular mononuclears, namely, the lymphatic glands, the spleen, and the lymphoid structures of the digestive tract. The other group, represented by the myeloid tissue, is said to be the source of red blood corpuscles and granular polynuclear leucocytes. So sharp a distinction is no longer admissible. The researches pursued by me with Dr. Josué showed that view to be too sweeping as regards the bone-marrow. The histological examinations which I made with Weil tend to prove that the study of variola does not

confirm this dichotomy. Finally, in a highly remarkable series of researches, Dominici systematically studied the various hematopoietic organs of man and animals and demonstrated that the spleen may undergo a total myeloid transformation, as notably occurs as a result of repeated hemorrhages. He further demonstrated that vaccine virus causes the appearance of basophilic and amphophilic myelocytes and nucleated red blood corpuscles in the lymphatic glands.[1] It may, therefore, be concluded that the various lymphatic cells may originate in all the organs concerned in hematopoiesis. If, under normal conditions, each organ contains exclusively one sort of leucocytes, infection causes these seemingly fixed distinctions to disappear. Thus, cellular types, which were no longer found in the adult, reappear, indicating a return to conditions of fetal life.

The Bone-marrow in Infections.

Preliminary Considerations of Normal Anatomy and Physiology. The bone-marrow has long been considered a tissue filling up the interior of bones to give them solidity without increasing their weight. It is now known that it discharges in the economy numerous functions of importance. This new conception has been accepted with some difficulty. In fact, the cellular elements, which evidently represent the active part, diminish and disappear as the individual grows; fat takes their place, so that the marrow seems to lose all its functional importance. It comes to a state of rest. As soon, however, as a new physiological or pathological condition requiring the production of white or red blood corpuscles supervenes, the fat is absorbed, the cells proliferate, and in some instances finally become as numerous as in young subjects. Instead of the yellow color which the marrow presents in the adult, it becomes red, as in the beginning of life; it resumes the fetal character. Thus, histological examination may inform us as to the degree of activity of the bone-marrow.

It is known that the bone-marrow seems to be formed of fatty tissue in the adult. A more attentive study shows, however, that it is a tissue of well-determined texture. It contains two series of cellular forms; some are destined for the production of leucocytes, the other for the production of cells with hemoglobin.

[1] Dominici. Sur le plan de structure du système hematopoiétique des mammifères. Archives de méd. expér., July, 1901.

The cells of the first series—*i. e.*, the myelocytes, generally measure from 14μ to 20μ, have the appearance of mononuclear leucocytes, but differ from them by the presence of protoplasmic granulations similar to those found in the polynuclear leucocytes of the blood. According to their tinctorial properties the granulations are divided into oxyphiles or eosinophiles, pseudoeosinophiles, neutrophiles, and basophiles. The neutrophile myelocytes are the most profusely distributed.

The bone-marrow likewise produces red blood corpuscles. It is possible to follow the various stages of the evolution of the nucleated red globules.

The bone-marrow seems also to be capable of producing, especially under pathological conditions, soluble substances; as the latter always proceed from cellular secretions, the proliferation observed in the course of diseases is favorable to this conception.

It is hardly necessary to recall the rôle played by the bone-marrow in the nutrition and regeneration of bones.[1] Finally, the marrow is capable of absorbing as well as of secreting. The experiments of Dubuisson-Christot demonstrated that substances introduced into the medullary canal of long bones rapidly pass into the general circulation, even more rapidly than when injection is made into the peritoneum or the liver.

Modifications of the Bone-marrow in Experimental Infections. The bone-marrow becomes the centre of defense for the organism in a number of infections and intoxications. This rôle, which we endeavored to elucidate in a series of researches published with Dr. Josue, had but rarely been studied before us. In December, 1896, we reported our first investigations on the state of the bone-marrow in suppurations, pointing out the important modifications in the structure and texture of this tissue.[2] Dominici,[3] proving the appearance of nucleated red globules in the blood of infected

[1] Ollier. De la moelle des os et de son rôle dans l'ossification. Journal de la physiologie, 1863. Goujon. Recherches expérimentales sur les propriétés physiologiques de la moelle. Journal d'anatomie et de physiologiè, 1869.

[2] Roger and Josué. Recherches expérimentales sur les modifications de la moelle osseuse dans les suppurations. Soc. de biol., Dec. 12, 1896, p. 1038. Action de la toxine et de l'antitoxine diphtériques sur la moelle osseuse, ibid., Jan. 9, 1897. Des modifications histologiques et chimiques de la moelle osseuse aux différents âges et dans l'infection staphylococcique, ibid., March 25, 1899. Des modifications histologique chimiques de la moelle osseuse dans l'inanition, ibid., May 5, 1900.

[3] Dominici. Tumeur de l'ampoule de Vater. Soc. anat., 1896, p. 708. Septicémie exp. à globules rouges nuclées, ibid., 1896, p. 714.

rabbits, attributed this phenomenon to the reaction of the bone-marrow. About the same time Trambusti studied the bone-marrow of guinea-pigs in diphtheria and laid stress on the signs of functional activity which this disease imposed upon the cells of the marrow.

The reaction of the bone-marrow is expressed not only by cellular modifications indicating increased activity, but also by topographic changes easily noticeable on sections, even when examined by the unassisted eye. The marrow gives rise to blood cells endowed with phagocytic properties; consequently, when an increased number of these is required, the original cells or myelocytes, intermediate forms, even the polynuclears, are likewise increased in the medullary tissue. The latter is thus invaded by a tremendous number of cells.

By giving birth to the leucocytes, which will pick up, digest, and destroy pathogenic germs, the bone-marrow plays a rôle of prime importance in the defense of the organism; it supplies it with the army which will defeat the invaders. It is, therefore, at the moment of danger that this tissue displays the greatest energy.

The rôle of the bone-marrow thus seems to be more complex. Although there is no direct demonstration, it is highly probable that the marrow possesses secretory and antitoxic properties. This is indicated by the multiplication of medullary cells in the course of various intoxications and consecutively to the introduction of certain sera.

This reaction of the bone-marrow is observed in a great number of conditions. Staphylococcic infection, which was the first subject of our investigations, may be cited as an example.

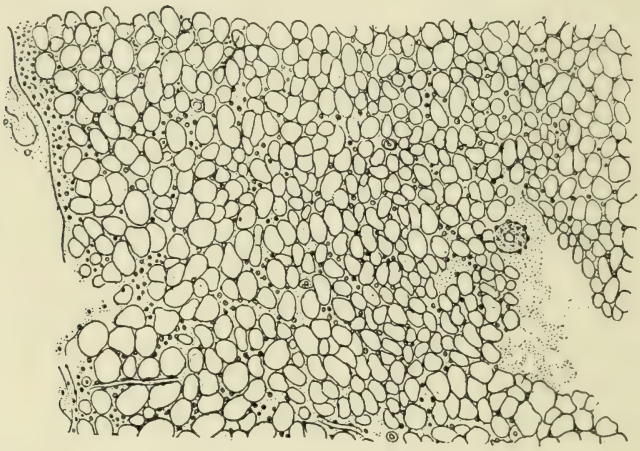
Modifications in the Bone-marrow in Experimental Staphylococcic Infection. In these experiments we employed adult rabbits weighing from 2000 to 3200 grams. We chose such heavy animals in order to be certain that their marrow presented the adipose type. In fact, it is known that the cellular elements, which are very abundant in the young, diminish with age and, in the adult, are replaced by fat.

If a culture of medium virulence be employed the modifications which result from a subcutaneous injection may easily be watched in the bone-marrow. Forty-eight hours after the injection of 1 c.c. of the culture, the local lesion—*i. e.*, suppuration—appears. At this moment leucocytosis is at its maximum; the leucocytes are found to number from 12,000 or 15,000 to 30,000 or 40,000 per c.mm. If the animal is killed the bone-marrow presents a red color, considerable congestion, and multitudes of red cells. The medullary

cells are also increased and particularly profuse in the peripheral parts.

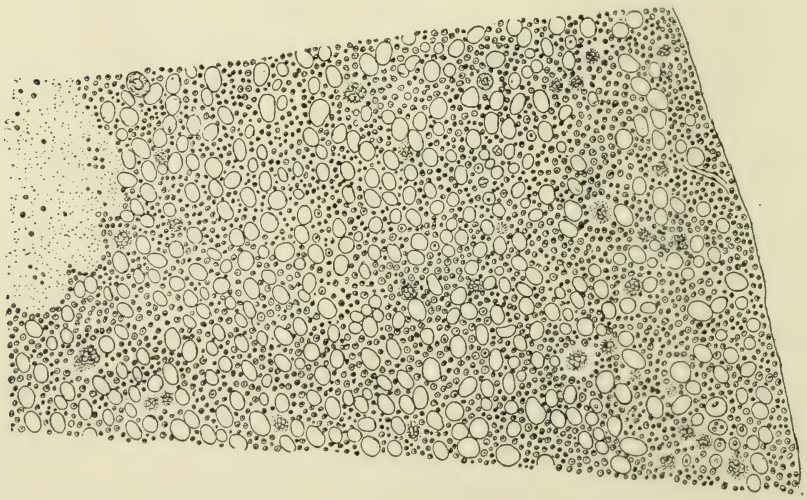
The modifications progress so that, on the fifth day, the marrow is constituted simply of cells mixed with red corpuscles and accumu-

FIG. 21.



Bone-marrow of a normal rabbit. On the left side, the sinus with its artery; on the right, the cortical layer. At the centre, the areolar tissue containing a small number of cells.

FIG. 22.



Bone-marrow of the rabbit in neutrophilic reaction. Considerable increase in the number of cells; diminution in volume of fatty areolæ.

lated in large numbers at certain points. There is nothing left of the normal arrangement, no more areolæ full of fat.

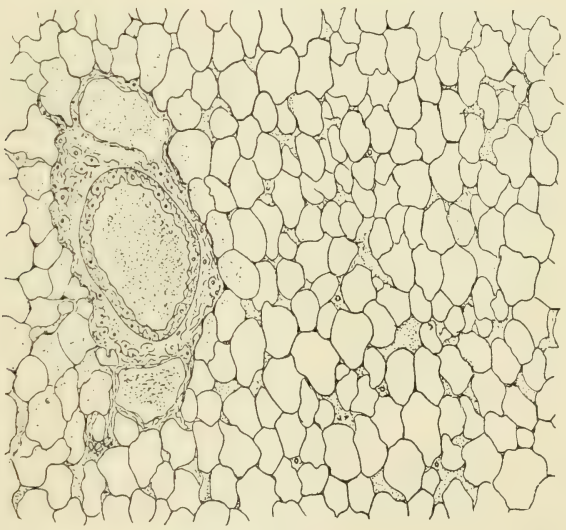
At the end of fifteen days retrogression of the process is observable; the normal conditions tend to reappear here and there; areolæ full of fat are again found, remarkable only for their smaller dimensions.

To sum up, all the cellular elements increase in number and size; they are in a state of intense activity. The inert elements, which, under normal conditions or rather in a state of rest, form the greatest part of the tissue, give way to the active elements.

A question may be raised here: May one variety of cells multiply in a predominant or exclusive manner? In other words, are there neutrophilic, eosinophilic, or normoblastic reactions?

In the first place, it is to be recognized that there is never an absolutely exclusive multiplication of cells. In the cases which we examined a certain degree of irritation and proliferation of other species existed. Likewise, in the neutrophilic reaction of suppurations and certain infections there is multiplication of other varieties of cells.

Fig. 23.



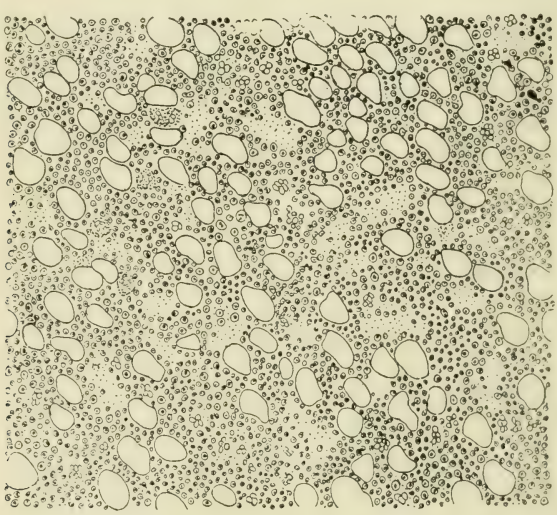
Bone-marrow of normal man. Sinus containing an artery. Few cells. Fatty areolæ of large size.

Reactions of the Bone-marrow in Man. The human bone-marrow seems to lose most of its activity at an early age. When, however, an intoxication occurs it again assumes the type observed in childhood; it resumes its functions in order to protect the organism. The cellular elements, which were extremely rare when the organs were not engaged in struggle, become very numerous. The reac-

tion, however, is less readily produced and less marked than in the rabbit.

Let us take, for example, the neutrophilic reaction of the bone-marrow in tuberculosis.[1] The proliferated bone-marrow is darker in color, softer, and at times pasty. Under the microscope it is seen that cellular proliferation is not at once progressing throughout the entire thickness of the marrow. The invasion by the cells is at first partial; their distribution is not clearly systematic. Even in the midst of proliferated parts there may be found fatty areolæ, though not so large as normal.

Fig. 24.



Human bone-marrow in neutrophilic reaction. Enormous increase in the number of cells; the areolæ are far less numerous and voluminous than normally. (Compare with Fig. 23.)

When considerably magnified all the cells are found to be increased in number, although the neutrophile myelocytes are predominant, mixed with all the intermediate series ending in polynuclears. The giant cells are not as large as in the rabbit. In the midst of all these elements are observed masses of pigment colored black by ammonium sulphydrate.

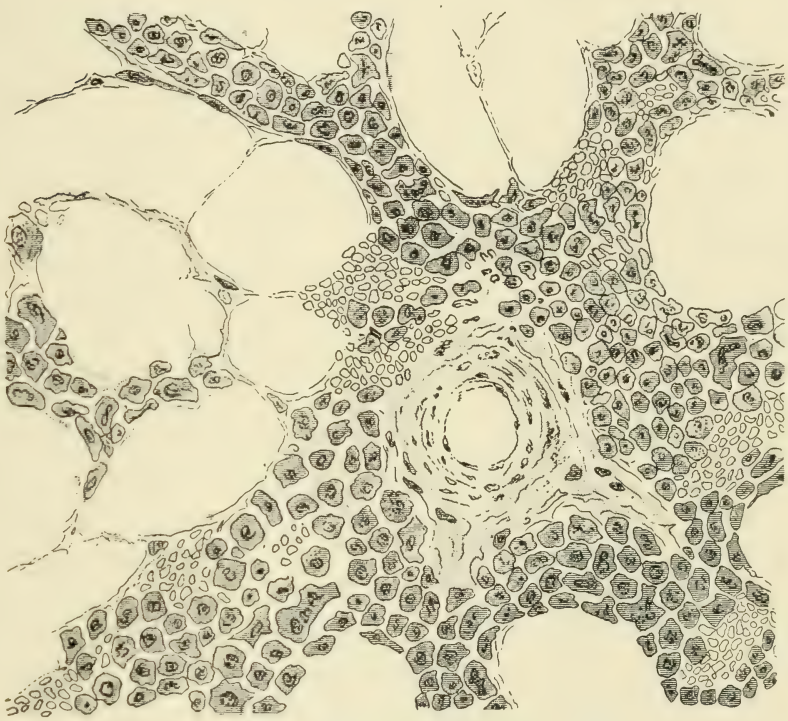
The Bone-marrow in Smallpox. The recent epidemic of variola in France offered an opportunity to take up this study and, by means of numerous improvements in fixation and staining, to complete and

[1] Josué. Moelle osseuse des tuberculeux et histogenèse du tubercule. Thèse de Paris, 1898.

modify in some respects the results already obtained. The researches of Dr. Courmont and Montagard[1] pursued coincidently with ours, and published only three weeks after our first note,[2] confirm the principal facts set forth by us.

In two cases of variola we noticed an absence of medullary reaction. This is an exception. At all events, however, the reaction of the bone-marrow manifests little intensity, at least in the adult. Our

FIG. 25.



Section of bone-marrow in variola. Moderate proliferation of cells confined to the area surrounding the vessels.

observations on this point are at variance with those of Golgi,[3] who laid stress upon the intensity of the reactionary phenomena which the bone-marrow presented in the cases studied by him. However, by comparing the results furnished by a topographic examination of the marrow with those obtained by counting the white corpuscles

[1] Courmont and Montagard. La moelle osseuse dans la variole. XIIIe Congrés international de médecine, Section de path. générale, Paris, August, 1900, p. 187.

[2] Roger, Josué, and Emile Weil. La moelle osseuse dans la variole. Soc. anat. July 13, 1900. Archives de méd. exp., September, 1900.

[3] Golgi. Sulle alterazioni del midollo del ossa nel vainolo. Rivista clinica di Bologna, 1873, p. 238.

on the eve of death we find an absolute concordance. Though the proliferation of the cells is poorly marked or *nil* in the medullary tissue, the number of leucocytes contained in the blood itself is not great, varying from 6000 to 8000, not exceeding 4428 in cases of confluent variola with terminal hemorrhages in which the bone-marrow was fatty.

The appearance of the bone-marrow in children suffering from variola is altogether different. The latter were all attacked by bronchopulmonary infectious complications. The marrow was red and invaded by large numbers of cells. The fatty areolæ had completely disappeared. The cellular formula in smallpox may be briefly laid down as follows: marked predominance of the mononuclears, relative diminution of the polynuclears. This is in accord with the findings of a qualitative examination of the blood, in which the polynuclears are likewise present in small numbers, while the mononuclears are more abundant than normally, and belong in part to different varieties which are not found under normal conditions: myelocytes, forms of irritation of Türck, etc.

The reactionary manifestations are the same in both pustular and hemorrhagic variola.

Lesions of the Bone-marrow in Infections. Apart from those modifications which occupy the undecided boundary between healthy and diseased conditions, since they indicate a struggle against a pathogenic agent, true lesions may also be observed in the medullary tissue.

An alteration, particularly frequent in acute infections, is characterized by disappearance of the nucleus, so that the cell forms no more than a uniform red mass. Such, for instance, is the case in experimental infection by anthrax.

There may also be found lesions of the connective tissue. Among these sclerosis is the most frequent. The sclerotic marrow often observed in tuberculous individuals may be taken as a type. It is yellow in color and firm. Sclerosis often coexists with cellular proliferation; the two lesions are then sharply separated and are produced in different regions of the medullary tissue.

The vessels at times present marked lesions of arteritis and phlebitis. In five children who suffered from chronic gastroenteritis and succumbed to bronchopneumonias, Haushalter and Spillmann found marked lesions of endarteritis and periarteritis.

Finally, miliary tubercles may develop in the medullary tissue in

cases of acute tuberculosis. These tubercles present the ordinary structure, and may be reproduced experimentally by inoculating cultures of the tubercle bacillus into the bone-marrow.

Semiology of the Bone-marrow. The study of modifications in the bone-marrow presents considerable importance from the standpoint of general pathology. It reveals one of the defensive procedures of the organism. It may appear less interesting from a clinical standpoint. The increased activity of the bone-marrow may, however, explain certain painful sensations experienced in the course or in consequence of infections in the limbs, especially in the juxta-epiphysial regions. It likewise accounts for the overgrowth of young subjects in consequence of certain diseases, notably typhoid fever. It may even be questioned whether certain osseous deformities, certain lesions of the skeleton, are not the consequence of the morbid process of which the bone-marrow is the seat. Are not the osteopathies of pneumonia, the osseous lesions of dyspeptic persons, and notably the nodules of the second phalanges, connected with lesions of the medullary tissue? Is not this tissue responsible for the development of rachitis and osteomalacia?

That these remarks are not baseless is shown by the results yielded by the study of typhoid fever. Various osteomedullary manifestations have been observed as a result of this infection.[1] Among the milder phenomena are the dull pains similar to those felt in the so-called "fever of growths." It is probably due to the action of diffused toxins. At a higher degree the patient complains of a fixed pain which is the clinical expression of a microbic colonization. Either resolution occurs or an exostosis develops. Finally, if the microbe is more virulent, a focus of osteomyelitis is produced, at times so slowly as to simulate a cold abscess.

A similar series of evolution is observed in a chronic infection, viz., syphilis. Pains in the bones, exostoses, and gummata equally point to an important participation of the medullary tissue.

The osteomedullary tissue may be the starting point of embolic accidents. Osteomyelitis, proliferative inflammations of the bone-marrow, liberate a certain amount of fat. This substance enters the circulation, and, being arrested in the capillaries, notably in those of the lung, may give rise to grave disorders.

The clinical study of the bone-marrow must be completed by

[1] Achard. Manifestations osseuses de la fièvre typhoïde. Semaine méd., 1899, p. 345.

hematological examinations. These examinations, by showing a great number of myelocytes, enable us to affirm involvement of the marrow. Two diseases in particular cause the passage into the blood of these peculiar cells, which are never encountered therein under normal conditions. One of them is lymphadenia, the influence of which has long been known; the other is variola, which gives rise to a myelocytosis so very characteristic that it may aid in establishing a differential diagnosis.

The Spleen in Infections.

The important rôle played by the spleen in the defense of the organism has only recently been understood. It appears now demonstrated that this gland exerts a destructive action upon living parasites and organic particles. Its chief function, however, is to supply to the circulation, and thus send to distant parts of the economy, cells capable of struggling against infectious agents. In addition to this phagocytic rôle related to its richness in morphological elements, the spleen may also aid in modifying the chemical constitution of the blood; it produces germicidal substances. This protective rôle, however, important as it is, cannot be said to be indispensable for the economy. Animals devoid of a spleen are still capable of resisting infection, because there are many other organs endowed with the same function. We shall cite but one example: In variola, the reactionary modifications in the bone-marrow and in the spleen are analogous; the same cells are produced by both organs.

Infectious diseases almost constantly affect the spleen and in most cases cause hypertrophy of this organ. This law suffers a few exceptions. The liver is not altered, at least its volume is not increased, in yellow fever, dysentery, and cholera; it is possible, however, that its parenchyma does undergo modifications which require minute investigations for their discovery.

The state of the spleen in typhoid fever has been a subject of particular attention. Morgagni noted the hypertrophy of this organ in the course of febrile diseases which may easily be related to typhoid fever. Some authors went so far as to regard the alteration of this gland the characteristic feature of typhoid fever, and described epidemic and contagious splenitis. It is to be remarked, however, that the spleen is not alone altered, but the other hematopoietic glands are similarly involved.

As is known, hypertrophy of the spleen occurs in the middle of the first week of typhoid fever; it increases until the end of the second week, and may be accompanied by intraparenchymatous hemorrhages and terminate exceptionally in rupture of the organ. The hypertrophied spleen is at first firm, hard, and red. At this stage the dominant feature is congestion of the parenchyma, which is so intense at certain points as to produce small hemorrhagic foci. The cellular lesions are not pronounced. Siredey noted only a multiplication of the cells of the Malpighian corpuscles. In the second stage—*i. e.*, from the twelfth to the thirtieth day—the spleen in some cases remains firm and hard; oftener it is soft, and on section it presents small points which are due to the prominence of the corpuscles of Malpighi. The latter contain, as normally, lymphocytes. This variety is mixed, however, with numerous mononuclear and even polynuclear cells. The cells of the pulp are tumefied, voluminous, and generally filled with the detritus of red and white blood corpuscles. They have the characters of mononuclears, with a small nucleus situated at one of the poles of the cell. Finally, the pulp, like the corpuscles, contains nodules formed of necrosed cells.

These modifications, some of which represent reactions and others lesions of the organs, are not peculiar to typhoid fever; they are encountered, in various degrees, in the most varied infections, even in those which remain local.[1]

Among the infections which most frequently give rise to hypertrophy of the spleen we may cite typhus fever, acute tuberculosis, and the eruptive fevers, notably scarlatina.

Special mention is due to variola. Since the researches of Golgi and of Ponfick it is generally admitted that the appearance of the spleen is not the same in the suppurating and the hemorrhagic types of this infection. The organ is said to be hypertrophied in the former, while in the latter it is believed to be small, hard, and black. The examinations, however, made by Dr. Weil and myself during the last epidemic render this conclusion inadmissible. The hypertrophy of the spleen is related not to the clinical type, but to the intensity of reaction. For this reason it is more frequent in the suppurating type. Thus in sixteen fatal cases of confluent variola the spleen was hypertrophied sixteen times. In twelve cases of

[1] Bezançon. Contribution à l'étude de la rate dans les maladies infectieuses. Thèse de Paris, 1895.

hemorrhagic variola it was hypertrophied but four times. In none of the latter series, however, have we found any peculiar appearance. Contrary to Golgi's opinion, histological examination revealed no fundamental differences. What is truly characteristic of hemorrhagic variola is the presence of nucleated red globules. In brief, the modifications undergone by the cells of the spleen are similar to those observed in the other hematopoietic organs, notably in the bone-marrow. Under the influence of variola the spleen is thus found to contain cellular elements which exist there only during fetal life and which seemed to have disappeared forever shortly after birth. Infection has revived a past state.

Gerhardt has shown hypertrophy of the spleen to be of frequent occurrence in pneumonia. The same may be observed in erysipelas, which resembles pneumonia in certain features of its evolution. Finally, the spleen is small in the algid period of cholera; it becomes voluminous if typhoid manifestations supervene.

Chronic infections do not spare this gland. It will suffice to refer to what occurs in syphilis during the secondary period, and more especially in malaria.

It is well to note that in all the organs and tissues in which pigment is encountered the latter is found in the vessels. In the spleen and bone-marrow, however, the pigment occupies the cells. It is in these localities that it seems to take its origin at the expense of red blood globules altered and destroyed by the hematozoa of malaria.[1] In this connection recurrent fever deserves special mention. During the periods of apyrexia the spirilla accumulate in the spleen, while the other viscera are free from them. Metchnikoff and Soudakewitch,[2] who pursued researches on monkeys, have seen the parasites devoured by the macrophages of the spleen. This is a highly remarkable example of phagocytosis. This result seems to be confirmed by the experiments of Soudakewitch, who learned that monkeys deprived of their spleens, unlike normal monkeys, succumbed to inoculation of the spirilla. This has been contradicted by Tiktine, who repeated the experiments and denies all influence to splenectomy. He thinks that the different results obtained by the former experimenter are due to the fact that he operated in winter, when the slightest lesion is sufficient to cause death to monkeys.

[1] Kelsch and Kiener. Traité des maladies des pays chauds. Paris, 1889.

[2] Soudakewitch. Recherches sur la fièvre récurrente. Annales de l'Institut Pasteur, 1891, p. 515.

The highly interesting work of Courmont and Duffau[1] teaches us that the resistance of animals varies considerably according to the microbe employed and the time elapsed since the extirpation of the spleen. If the pyogenic staphylococcus is employed the extirpation first diminishes the resistance of the animals—rabbits, dogs, etc.; subsequently it increases it. With the streptococcus the results are diametrically opposed to the former: animals in which the spleen had been extirpated two to eight days proved more resistant than the controls; on the contrary, those which were operated upon twenty-seven to forty-eight days after splenectomy proved to be more susceptible. Lastly, with the bacillus pyocyaneus the animals operated upon succumbed more rapidly whatever the date of operation. These experimental facts indicate once more the danger of hasty generalizations and explain a certain number of contradictory results.

Role of the Spleen in the Production of Germicidal Substances. In order to explain the action of the spleen upon microbes the modifications in phagocytosis were first invoked. Such was the opinion of Gamaleia. The same view was held by Bardach. As is known, the latter author contends that extirpation of the spleen lessens the resistance of animals by suppressing an important centre of microbic destruction. He finds confirmation of his ideas in the following experiment: He injected charcoal powder into the veins of four dogs. Two days later he inoculated the animals with 1 c.cm. of an anthrax culture; all the dogs succumbed, and microscopic examination demonstrated that the cells of the spleen, liver, and bone-marrow were crowded with charcoal particles, and therefore were absolutely incapable of ingesting the microbes.

At the time these first researches were published the protective action of the blood serum was scarcely recognized. Since innumerable investigations demonstrated beyond doubt the importance of germicidal properties of the fluids of the organism, the question concerning the spleen has been taken up. The researches of Hankin[2] proved the presence in the spleen of a strongly germicidal globulin. Montuori next undertook this new problem,[3] and reported highly

[1] Courmont and Duffau. Du rôle de la rate dans les infections. Archives de méd. expérim., 1898, p. 431.

[2] Hankin. A bacteria-killing globuline. Proc. Roy. Soc., London, xlviii. p. 93.

[3] Montuori. Influenza dell ablazione della mitza sur potere microbicida del sangue. La Riforma med., 1893, i. p. 472 and 485.

interesting facts which throw light on many obscure points. His experiments demonstrated the hematopoietic function of the spleen. This gland may, however, be supplemented by other organs, since, a few months after extirpation of the spleen, the blood regains its germicidal power. Montuori completed his experiments by investigating the chemical modifications which occur in the blood of animals with extirpated spleens. He recognized that the bactericidal power of the normal blood is due, as was shown by Ogata, to a true ferment. This ferment, which is very abundant in the blood of the spleen, is absent from the blood which has lost its germicidal power as a result of splenectomy.

While animals deprived of the spleen are more sensitive to certain viruses, they become more resistant to others. In the latter case the germicidal power of the blood increases and acquires the property of depriving microbes of their virulence. By making comparative cultures of the staphylococcus in the blood of normal animals and others without spleens Courmont and Duffau established that the microbe develops better and becomes exalted in the serum of those animals in which the spleens were extirpated. With the streptococcus the results were reversed; the microbe was attenuated. On the other hand, Blumreich and Jacoby found that the serum of splenectomized animals diminished the virulence of pyocyaneus diphtheria and cholera bacilli, and this power of the blood accounts for the increased resistance observed when splenectomized animals are inoculated. It is to be noted, however, that the chemical modifications of the fluids are not the only factors to be taken into account; the authors attribute an important influence to the increased leucocytosis which coincidently takes place.

The Lymphatic Glands in Infections.

The lymphatic system is provided with numerous protective organs, close follicles, and ganglia, which seem to play a double rôle: to arrest, retain, and modify the figurate elements and soluble products brought to them by the lymphatic capillaries; to pour into the blood cells and soluble products useful for the organism. In order to fulfil their functions the follicles and ganglia are arranged in chains, and are most numerously supplied to those regions most liable to microbic invasions. They are relatively less numerous at the root of the limbs, especially of the upper extremities. Their number in the lower extremities is particularly multiplied with a

view to protect the economy against the bacteria coming by way of the external genital organs and margin of the anus. Likewise, the follicles at the base of the tongue, pharynx, and tonsils form a lymphatic ring with the function of combating the bacteria of the mouth and throat. Less abundant in the esophagus and the stomach, the lymphoid organs are distributed with great profusion throughout the intestine, where they constitute the solitary follicles and Peyer's patches. In the appendix, which is most liable to attacks of infectious agents, the lymphoid system is most richly developed, forming a veritable glandular mass which has justly been compared to the tonsil.

Beyond this first line of defense are situated the glands, which represent as many fortresses ranged one behind the other. It is interesting to note that their number is in proportion to the danger of infection in each region.

The multiplication of the ganglia around the bronchi, at the root of the lungs, and especially in the mesentery, is particularly notable.

In a great number of circumstances bacteria of all kinds may pass through the skin and particularly the mucous membranes. They are arrested by the ganglia, in which they sojourn without giving rise to any reaction or disturbance. Loomis and Pizzini discovered tubercle bacilli in the tracheobronchial and mesenteric glands of apparently normal individuals. Manfredi and Perez[1] examined the lymphatic glands in eighty-five animals and detected bacteria in seventy-five of them. The same researches made upon three human cadavers gave positive results in each case. The subcutaneous glands are those most commonly infected; next, the tracheobronchial glands, while the mesenteric glands are generally sterile. Among the species most frequently met with are various sarcinæ, the staphylococcus aureus or albus, the mesenteric bacillus, a pseudotyphoid bacillus, etc.

The microbes enclosed in the lymphatic glands undergo notable alterations. Manfredi demonstrated that they gradually lose their virulence and are finally destroyed through a peculiar procedure which seems to be different from the means employed in other parts of the organism, but which is not yet well understood. These modifications are slowly effected. Not infrequently, therefore, the germs may persist for a long period of time, this period varying with the

[1] Perez. Modo di comportarsi del sistema ganglionare linfatico rispetto ai microorganismi. Labori di Laboratorio, publicati dal L. Manfredi, Palermo, 1897, vol. iii.

microbe and the animal employed in the experiment. For instance, the staphylococcus aureus survives forty days in the guinea-pig and thirty days in the dog. It is interesting to note that all other parts of the organism no longer contain any microbes, while some are still present in the lymphatic glands. This persistence of germs explains certain relapses, notably those of erysipelas. I believe the same fact accounts for the morbid incidents occurring during convalescence from scarlatina. The anginous lesions which characterize the onset of this infection permit the penetration of the buccal streptococcus into the lymphatic network; the cervical glands are congested. Later, at the moment of convalescence, a new infection of ganglionic origin may occur; then the patient has fever and complains of painful adenopathia. In some cases the ganglionic infection remains uncomplicated; in other instances it is followed by more or less serious events, and notably an attack of nephritis.

The lymphatic glands, like all the dependencies of the lymphatic system, are especially developed during childhood. In fact, it is at this period of life that the danger of infection is greatest. The lymphatic system is, therefore, most vigilant and enjoys its greatest functional energy. The slightest lesion causes ganglionic congestion. When an agent is highly pathogenic it freely traverses the lymphatic system and produces a general infection without the development of any adenopathy. The latter manifestation is likewise wanting or remains unnoticed when the agent is but slightly virulent. It is in infections of medium intensity, therefore, that the ganglionic phenomena must be studied. The development of adenopathies depends upon two factors: the nature of the pathogenic agent and the state of the individual. With individuals whose organisms are incapable of energetic reaction, adenopathy is little marked; it is insufficient. In the contrary case, especially in children, it is too energetic and expressed by lesions which survive the cause, and may give rise to numerous incidents during and after the infectious process; such, for instance, is the case in tracheobronchial adenopathies compressing the respiratory passages and the nerves of the neighborhoods.

Histological Study. The presence of bacteria causes in the lymphatic glands modifications well studied by Drs. Bezançon and Labbe, who have made numerous experiments on this subject. The effects vary according to the activity of toxins. If the latter are of medium energy, reactionary phenomena are produced. If

they are extremely energetic, necrosis occurs, at times with astonishing rapidity. In fifty minutes the diphtheritic toxin gives rise to cellular degenerations and fibrinoid exudates. If a little serum be injected at the same time or twenty-four hours previously, reactionary phenomena appear (Bezançon and Labbe).

The reactionary phenomena are grouped under three divisions: congestion, proliferation of the fixed cells, and arrival of polynuclear cells.

Congestion is at times so intense as to provoke hemorrhage. Such is the case, particularly, in pneumonia, anthrax, and diphtheria. The fixed and endothelial cells soon become swollen and form macrophages, which mingle with the leucocytes, while the lymphocytes continue to multiply in the follicles by karyokinesis. At the same time the polynuclear cells arrive. It is known that the gland contains normally no other than polynuclear cells and lymphocytes. The polynuclears arrive through the afferent lymphatics vessel and the bloodvessels—*i. e.*, the capillaries. This leucocytosis occurs early; it appears three-quarters of an hour after bacterial inoculation, then it increases progressively, to again decline toward the eighteenth hour. These modifications are especially marked in the glands corresponding to the invaded point, but also occur with the same characters in distant glands, only with less intensity.

Beside these defensive reactions we must note the necrotic process. The cells undergo hyaline degeneration, especially in slow cases. The dilated lymphatic channels are filled with pale, large cells with a vitreous protoplasm and a colorless nucleus. The polynuclear leucocytes that have migrated into the glands are also involved, though in a different manner; their nucleus is fragmented and reduced to fine granules. The follicular system, the most resisting part, also finally undergoes degeneration, notably in diphtheria. Lastly, the bloodvessels undergo arteritis and hyaline degeneration, and their lumina may become obliterated by thrombosis.

The inflamed gland may gradually recover its normal condition or remain enlarged. In the latter case it occasionally assumes the appearance of a tubercular lesion, but seems to be due to the persistence of pyogenic cocci. In other instances the process proceeds to suppuration. All parts of the gland are not invaded simultaneously; the follicular system resists for a long time.

Finally, the diseased cells may not be replaced, and then the inflammatory lesion terminates in sclerosis.

Adenopathies in Variola. We cannot review all the infections which affect the lymphatic glands. We must, however, direct the attention of the reader to variola, which, from the standpoint under consideration, is extremely important, and which has hitherto been overlooked. The only work on this subject is Lelandxis' thesis, inspired by Empis. The frequency of ganglionic hypertrophy in variola has been pointed out by this author, who considers it an element of favorable prognosis.

The investigations which were pursued with Dr. Weil during the late variola epidemic in Paris showed us that enlargement of the lymphatic glands is subject to the same rules as hypertrophy of the spleen. It is very marked in pustular types of smallpox, very slight or *nil* in hemorrhagic types. The enlarged glands are generally painless, and hypertrophy is apparent from the beginning of the disease, increases during the period of eruption, persists during suppuration, and then declines and disappears. The axillary and inguinal groups are most frequently involved, although the topography of the exanthema does not explain this localization.

The histological features peculiar to variolar adenopathy are the presence in the lymphatic vessels and around the follicles of cellular forms similar to those found in the bone-marrow, notably neutrophilic myelocytes, a few basophilic myelocytes, and, in some instances, eosinophilic myelocytes. Finally, a few giant cells, and, in hemorrhagic types, nucleated red corpuscles may also be encountered. This peculiar evolution (which had hitherto been observed only in leukemia) may extend to the cellular tissue surrounding the glands. In sections its appearance is similar to that of the bone-marrow. The latter fact further emphasizes the analogy of the process to that which occurs in leukemia. It may, therefore, be assumed that the cellular tissue itself acquires a cytogenetic activity, and that, like the spleen, the glands, and the bone-marrow, it produces various leucocytes. This process has not thus far been observed in any other infection than variola. It would be interesting to take up the question from a general standpoint and investigate the state of the connective tissue in all infections. I am convinced that very pronounced modifications will be observed.

Syphilitic and Tubercular Adenopathies. Chronic infections often give rise to ganglionic lesions. Syphilis is a familiar illustration. The chancre produces enlargement in a group of lymphatic glands among which one becomes remarkable for its size. This

adenopathy is lacking only in exceptional and generally very grave cases. During the secondary period multiple adenopathies occur and are of considerable semiological importance. They often coincide with hypertrophy of other parts of the lymphatic system, especially in women, whose tonsils and spleens become likewise enlarged. During the tertiary period germs may be found in them, these germs presenting no particular character of evolution.

Tubercular adenopathies may be generalized. This condition is mainly observed in young children. Micropolyadenitis is strongly suggestive of tuberculosis and more readily detected than hypertrophic conditions of the liver and spleen. This peculiar evolution is comparable to what is observed in laboratories. Tuberculosis caused by inoculation into guinea-pigs behaves in exactly the same manner. It is first expressed by tumefaction of the glands corresponding to the infected point, and then all the glands of the economy are gradually involved, and finally the abdominal viscera. In some cases the thoracic organs also are affected. The lymphatic system is thus seen to be well designed to arrest the course of invading bacteria, although in some rare instances it may aid in their spread, as is shown by the investigations of Ponfick on the thoracic duct.

It is interesting to remark that actinomycosis, a disease so closely allied to tuberculosis, does not affect the lymphatic glands.

Humoral Modifications of Lymphatic Origin. It is not merely by phagocytic action that the lymphatic glands protect the system. It seems to be demonstrated that these small organs secrete germicidal and antitoxic substances. The investigations of Pfeiffer and Marx show that, during the immunization of animals, these glands produce antitoxins which are carried into the circulation. It is conceivable that the glands of infected or vaccinated animals may be utilized in the treatment of certain diseases. Manfredi has made some attempts in this direction and found that the ganglionic juice of tuberculous goats hindered the development of this disease in guinea-pigs.

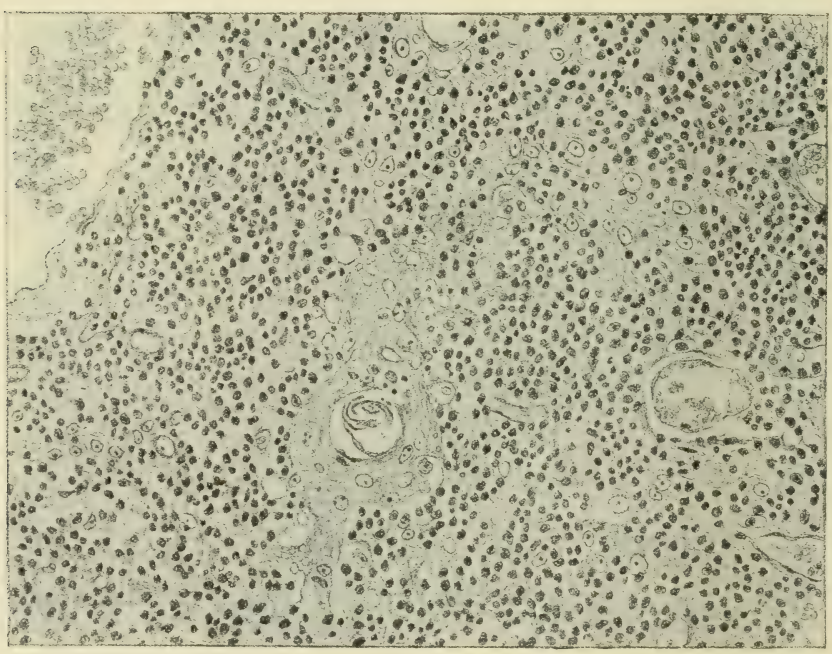
The Thymus in Infection.

Anatomical and Physiological Considerations. In its histological structure the thymus resembles the lymphatic glands. It differs from them in its embryogenic origin.[1] The thymus has at

[1] Ghika. Etude sur le thymus. Thèse de Paris, July, 1901. This is a very complete monograph containing a great number of histological and experimental researches pursued in our laboratory.

first an epithelial structure; later it assumes a lymphoid character as a result of direct transformation of the primary elements. We found this transformation completed in a fetus of three months. In the fetus of six months appear peculiar formations—the corpuscles of Hassall—the aspect of which is absolutely characteristic. From the sixth month onward and until the period when regression sets in the thymus undergoes no appreciable modification in structure. The cells contained in the fibrillary network are mostly lymphocytes; besides these there are also some neutrophilic and fewer eosinophilic

FIG. 26.



Normal cat, one month. Reticulum quite visible. Numerous lymphocytes. Trabecular cells with large clear nucleus and distinct nucleolus. Large corpuscles of Hassall. Epithelioid fragments in the centre. Numerous vessles filled with blood corpuscles.

polynuclears, non-granular mononuclears, mastzellen, granular mononuclears or eosinophile, basophile, or neutrophile myelocytes, rarely giant cells, and elements resembling nucleated red globules. Finally, there are also epithelioid cells and large cells with vesicular nucleus.

Hassall's corpuscles have an extremely variable appearance. They are occasionally formed by a single enormous cell; the chromatin of the nucleus presents the most varied figures.

The thymus grows smaller with age. It is soon invaded by a profuse cellulo-adipose mass, but does not completely disappear. The corpuscles persist for a long time, but disappear in the very aged.

In animals this gland presents a structure very much similar to the human. The same cellular forms are found; the only essential difference is in the number and appearance of Hassall's corpuscles. In the rabbit, guinea-pig, and rat these corpuscles are extremely rare, and are composed mostly of a single large cell. The cat, on the contrary, has very clear corpuscles, and while it is always easy to differentiate in sections a thymus of a child from that of a rabbit, guinea-pig, or rat, it is almost impossible to distinguish the human thymus from that of a cat. In frogs and hibernating animals the thymus is voluminous in the summer and small in winter. Pathology teaches us that this gland, which is highly developed in well-nourished children, atrophies in feeble or cachectic children. Is the atrophy the cause or the effect of the nutritional disorders?

To solve this problem experimentation should be resorted to. A great many times, therefore, the gland has been extirpated. On the other hand, attempts have been made to ascertain the effects of injection, ingestion, and inoculation of extracts of this gland. Without wishing to dwell upon the details of the experiments related in the thesis of Dr. Ghika, we believe that facts warrant us in concluding that the thymus plays an important part in nutrition. In order to obtain clear evidence very young animals must be operated upon. Our best experiment was made upon a cat fifteen days old. The extirpation of the thymus was complete. The animal, which weighed 485 grams, increased in weight to 635 grams in twenty-two days. An animal of the same litter, kept as control, weighed then 890 grams. From this moment onward the operated one began to lose flesh. At the end of thirty-five days it succumbed in a state of profound cachexia. It then weighed 430 grams, 55 grams less than at the beginning of the experiment, while the weight of the control reached 1090 grams.

Among the symptoms observed in animals in which the thymus is extirpated we may mention, besides emaciation, arrest of growth, anomalies of the skeleton, especially costal deformities, trembling, stupor, weakness, and, in some cases, paralysis. These various manifestations may be slight or absent as the result of supplemental activity on the part of other hematopoietic organs, at least in certain cases. At the necropsy of the animals experimented on we found

the bone-marrow red and proliferated; histological examination demonstrated its vicarious activity.

Besides being a gland with an internal secretion the thymus has an important cytopoietic function. Its structure, being similar to that of all adenoid tissues, leads to the conclusion that it forms white blood corpuscles. The experiments pursued on this question have not given very clear results, probably because other hematopoietic organs rapidly come into play and prevent the development of manifestations.

Histological Modifications of the Thymus in Infections. The histological study of the thymus leads to clearer conclusions. In a great variety of physiological or pathological circumstances cellular proliferations entirely comparable to those occurring in the bone-marrow are observed.

Cellular proliferation takes place in inanition, intoxications, and infections. We have been able to study these in animals intoxicated by phosphorus or carbonic oxide as well as in those inoculated with the most varied microbes or poisoned by the toxin of diphtheria. We have found the same modifications in the thymus glands of children dead from variola, measles, erysipelas, whooping-cough, syphilis, and tuberculosis.

This study of modifications of the thymus in infections is entirely new.[1] The only information found in authoritative works consists of a few macroscopic examinations. From these it might be inferred that the thymus does not react in infections or that it occasionally undergoes partial degenerations. This opinion does not seem to us acceptable. The thymus is constantly modified in the course of various infectious processes. It may be seen with the naked eye that the gland is enlarged, red, and congested. It may even be the seat of hemorrhages. In other instances it may be pale and anemic. Under the microscope modifications in the fibrillary network, vessels, cells, and Hassall's corpuscles can be seen. The fibrillary substance is only slightly affected, at least when the process is acute. In some cases it becomes thickened. The bloodvessels are congested, and their walls are often infiltrated with yellow cells. At certain points thromboses and hemorrhages are observed. The principal modifications are found in the cellular elements. The lymphocytes

[1] Roger and Ghika. Recherches sur l'anatomie normale et pathologique du thymus, XIIIe Congrés intern. de médecine, section de pathologie générale, p. 219. Journal de phys. et pathol. générale, Sept., 1900.

and the small mononuclears always form the fundamental part of the gland. But a greater number of large mononuclears, intermediate forms, and polyneutrophiles are met with. The polyeosinophiles and nucleated red globules are also more numerous. Moreover, there appear elements which are either absent or rare in the normal thymus—mastzellen, myelocytes, leucocytes with mixed granulations, and, in animals, pseudoeosinophiles. There are also encountered two special varieties of non-granular mononuclears. Some are large cells measuring from 15μ to 20μ, with volumin-

FIG. 27.



Child of two months, dead from erysipelas of the face. Recent exudate dissociating the lymphocytes. Numerous granular forms. Cystic Hassall's corpuscles with colloid contents in the form of onion bulbs, unicellular or paucicellular.

ous excentric nucleus; the protoplasm stains strongly with thionin, but faintly, if at all, with eosin. The others are equally large cells with a dark protoplasm and hardly visible nuclei. The former resemble plasma cells, the latter the irritation cells of Türck.

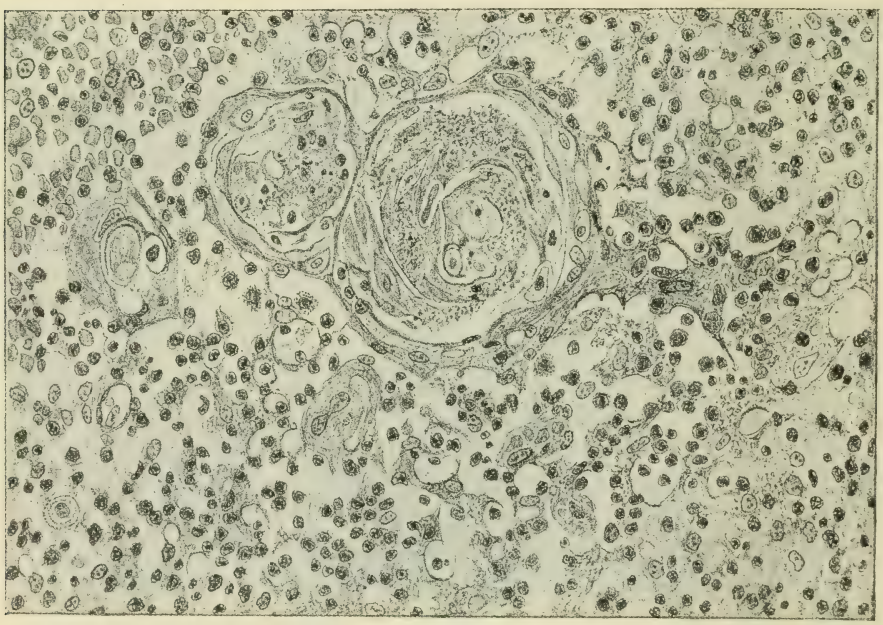
Besides these functional modifications, lesions also occur. The cells may undergo granular, vacuolar, or fatty degeneration, coagulation necrosis, and karyolysis. At times necrotic foci are formed in which all the elements are destroyed.

All infections do not act with the same intensity, but all do act.

Erysipelas is one of the diseases the action of which is most marked. The thymus is remarkable for the development of numerous granular myelocytes.

Histological examination of a certain number of thymus glands always reveals the existence of sclerotic lesions in some of them. Ghika examined sixty-four glands, and found sixteen of them sclerosed. In eleven of the cases the lesions were very pronounced.

FIG. 28.



The same preparation as in the preceding figure, more highly magnified. Very large corpuscles of Hassall, containing cells, cell fragments, and colloid substance. The wall is formed of epithelioid cells, which are clearly continued on the right side with the trabecular cells. In the left lower corner is seen a large cell composed of a clear nucleus and rounded protoplasm, containing fine eosinophile granulations disposed in concentric circles.

These sclerotic lesions of the thymus are occasionally observed in children dead of acute diseases. In such instances it is quite certain that the lesions existed previous to the occurrence of the acute malady. They sometimes depend upon involution of the gland. When, however, the lesions are found in young children they must be attributed to syphilis or some antecedent infection, to bad hygiene, athrepsy, or some hereditary taint. Syphilis, tuber-

culosis, alcoholism, and defective nutrition of the parents are the most frequent causes.

Primary Infection of the Thymus. Although the thymus is almost invariably affected in the course of infectious diseases, it is seldom the seat of a primary affection. There are but few facts on record.

W. Wittich has reported the case of a young man, aged eighteen years, who was suddenly seized with dyspnea and retrosternal pain, and who was soon attacked by hydrothorax and ascites. He succumbed to a paroxysm of dyspnea. The autopsy revealed an enormous thymus filled with purulent cavities. The pericardium was healthy. Demme published a similar case. In a child of two and a half months was found a purulent transformation of the thymus, which was manifested during life by a red and painful tumor occupying the lower part of the neck. Schlossmann, Helm, and Biedert have recorded cases of rapid death preceded by paroxysms of suffocation in young children. The necropsy showed a voluminous, inflamed thymus (Biedert), or one infiltrated with pus. In Schlossmann's case bacteriological examination revealed a microbe analogous to Fischer's pyobacterium. Demme has related an incontestable case of primary tuberculosis of the thymus in a little girl. Syphilitic gummata and sclerosis may develop in this gland as well as in any other organ.

The Thyroid Gland in Infectious Diseases.

The only lesion of the thyroid that has been described in infections is suppurative thyroiditis. This involvement is so rare that, if it was the only one that may occur, the participation of this gland in infectious processes should be regarded as exceptional. Systematic examination of the thyroid in all the necropsies which we made during one year led us to a different opinion. Far from being indifferent in the presence of infection, this gland always reacts more or less energetically, and this reaction is expressed by histological modifications which we have studied with Dr. Garnier.[1] Let us first briefly consider certain details of normal histology.

[1] Roger and Garnier. Infection thyroïdienne expérimentale. Soc. de biol., Oct. 12, 1898. Action du bacille typhique sur la glande thyroïde. Ibid. La glande thyroïde dans les maladies infectieuses. Presse médicale, April 19, 1899. Recherches expérimentales sur les infections thyroïdiennes. Ibid., August 9, 1900.

Remarks on Normal Histology. The thyroid apparatus is composed in man, as in other mammals, of two distinct parts—the thyroid gland proper, described in all classical treatises, and the parathyroids—small glands discovered by Sandström in 1880, the physiological importance of which was proved by Gley in 1892.

The structure of the thyroid is not the same in the adult and in children. Defaucamberge was the first to show this difference in

FIG. 29.



Thyroid gland in children. This figure and the following three are taken from the work which we published with Dr. Garnier (La glande thyroide dans les maladies infectieuses), Presse médicale, April 19, 1899.

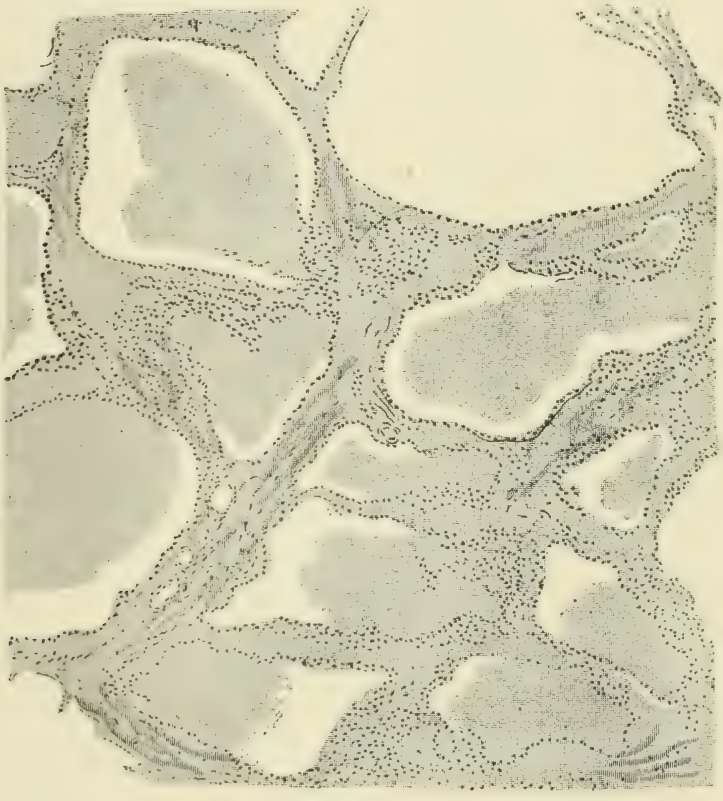
1889, and distinguished two types: the truly glandular type, which is found in the child and is more or less marked until puberty, and the colloid type, which corresponds to the normal state in adults. The thyroid gland in children is formed of distinct lobules, separated from each other by connective tissue. (Fig. 29.)

This tissue enters the lobules and divides them into smaller departments, each of these containing two or three vesicles. The connective

tissue contains numerous nuclei and an abundant basement substance. Each vesicle is lined by a layer of lowly organized cells; the centre is occupied by colloid matter.

In the thyroid gland of the adult the most striking feature is the complete absence of the lobulated structure. (Fig. 30.) The not abundant connective tissue is reduced to fine trabeculæ running between the vesicles. The glandular parenchyma appears to be

Fig. 30.



Thyroid gland of a normal adult.

formed simply by juxtaposition of closely arranged colloid masses, or is separated here and there by a cellular mass.

The *parathyroids* are small organs situated in the neighborhood of the thyroid, but differing from it in origin and structure. They are chiefly met with near the point at which the thyroid arteries enter the gland. They vary in number and size. They do not present the vesicular arrangement or the colloid substance of the thyroid. They are surrounded by a capsule of connective tissue

covering the whole gland and extending into its interior partitions, which divide it into irregular departments. The meshes thus formed are filled with rows of cubical epithelial cells with well-stained nuclei and surrounded by a profuse granular protoplasm. These cells are pressed one against the other and exactly applied on the one hand to the connective tissue wall and, on the other, to the neighboring row.

FIG. 31.



Thyroid gland of a man dead from scarlatina. Considerable dilatation of vessels. Trains of colloid matter surrounding the vesicles.

General Characters of the Thyroid in Acute Infections. When examined with the naked eye the gland appears enlarged. While normally its weight is about 25 grams (1 ounce), we found it in seven cases to reach from 37 to 71 grams ($1\frac{1}{2}$ to $2\frac{1}{2}$ ounces). The color is changed from its normal hue—that is, yellowish—into red, sometimes blue. The connective tissue is only slightly modified and usually undergoes no pronounced alteration. At times, how-

ever, especially in children, it seems to contain a greater number of nuclei than normal. The presence of colloid substance outside the vesicles changes the general appearance of the gland and may lead to the belief that the connective tissue is hypertrophied. (Fig. 31). This colloid substance dilates the lymphatic spaces of the gland and produces a more or less complete network, the meshes of which are filled with vesicles. The vessels are dilated. There is sometimes arteritis and phlebitis. The inflammation of the vessels, however,

Fig. 32.



Thyroid gland of an adult dead from scarlatina. Lobule completely transformed; the vesicles contracted and crowded with cells; the thyroideal tissue is still recognizable by a few dilated vesicles at the border of the lobule; the colloid substance no longer takes eosin.

presents nothing particular. The vesicles are commonly smaller than normal. Their composition is often profoundly modified; some of them no longer contain any colloid substance, and their centre is occupied only by cells in course of degeneration. In many cases the protoplasm of several cells at the centre of the vesicle is fused in a finely granular mass in the midst of which are seen degenerated nuclei. On the other hand, some vesicles still contain a certain quantity of normal colloid substance in the midst of desquamated

cells. When the lesions are very marked (Fig. 32) the secretion of the colloid matter seems to be hindered or replaced by a few granulations.

We have histologically examined the parathyroids in three cases of scarlatina and in one case of diphtheria. Only in two of the cases were they found to be altered. The most important alterations were observed in the case of a woman who died from scarlatina. While the thyroid had deviated but little from the normal type, the glandules, four in number, presented interesting modifications. The connective meshes were half empty; the cells had lost the arrangement in regular rows and were found in masses at the centre of each mesh. They were often formed by granular protoplasm with poorly marked limits. The nucleus stained well. These lesions, although diffuse and encountered in all parts, did not involve the entire gland; on the contrary, certain portions remained perfectly healthy.

In a case of diphtheria the same appearance was found, but the lesions were more discrete.

It is well to remark that the frequency of thyroideal lesions varies considerably according to different infections. In scarlatina the thyroid is almost constantly the seat of profound alterations, while it resists far better in measles. In the case of a woman who died from confluent variola the gland was the seat of very pronounced lesions. It was hypertrophied and highly congested; small parenchymatous hemorrhages had also occurred.

Mechanism and Significance of Thyroideal Lesions. Torry[1] attributes to the thyroid gland a special destructive power against bacteria. This action, if real, cannot be considerable. The injections made through the carotid vessels are at least as effective as intravenous. On the other hand, rabbits subjected to thyroidectomy resist at least as well as normal rabbits. Moreover, under the influence of infections the thyroid is not spared; it presents the same alterations as the other parenchymatous structures. The reason the lesions in the thyroid are generally less pronounced than those in the liver and kidney is that the activity of the thyroid is slow in the adult. The first effect of infection is to arouse the torpid secretory activity; for profounder changes to be effected the action of the toxic product must be intense or long continued.

[1] Torry. La tiroide nei morbi infettivi. Il policlinico, March 15, April 15, and May 15, 1900.

In this connection experiments demonstrate that chronic infections give rise in most cases to interstitial lesions; intense infections, even when of short duration, produce chiefly cellular alterations. It may, therefore, be concluded that the extent and depth of lesions depend rather upon the energy than upon the persistence of the morbid processes. This law of general pathology is clearly demonstrated by experimental facts obtained by us. By injection of microbes into the thyroideal arteries we have been able to produce all degrees of visceral inflammation. By varying the dose or the virulence of cultures one may obtain thyroiditis with interstitial predominance—*i. e.*, hemorrhagic thyroiditis, thyroiditis with active leucocytic reaction and sclerosis, or thyroiditis with parenchymatous predominance, namely, acute necrosis and degeneration of the cells, or even epithelial proliferation terminating in neoplastic development.

These experimental data are interesting, since the same anatomico-pathological types may occur in man. Suppurative thyroiditis, which has long been noted, is to-day well known; it develops in the decline of various infectious diseases. Hemorrhagic thyroiditis is rare; it has been observed in variola by Liouville and ourselves. The other forms may be encountered in acute infections, though they never present the intensity observed in experimental inflammations. Thyroideal sclerosis is rather an incident of chronic diseases, such as tuberculosis. It may, however, appear in the course of the most varied infections when these are more or less prolonged.

How are the various parenchymatous modifications of the thyroid to be interpreted? Experimental pathology enables us to answer this question. If the infected thyroid be compared to glands the activity of which is excited by pilocarpine or iodine, the phenomena are found to be practically the same. Infection arouses the glandular activity, which is expressed by increased secretion. This is the first degree. When the process is more intense the colloid matter suffers qualitative modifications. Unlike what occurs in animals treated with pilocarpine or iodine, it undergoes a granular transformation and loses its normal staining capacity. Thus in the course of infectious diseases more or less marked secretory disorders in the thyroid, as in other glands of the economy, occur. After a period of overactivity a diminution or an alteration of functions appears. As the liver then secretes abnormal pigments, so the thyroid forms an atypical and peculiar colloid substance.

Although in the majority of cases the thyroideal lesions are slight and admit of sufficient reparation to permit the re-establishment of its functions, it is clear that such may not always be the case. Alterations may subsist which, at the end of a variable period of time, perhaps several years, having evolved on their own account, may be expressed by functional disturbances; for instance, myxedema and exophthalmic goitre may be connected with some previous infection.

The Suprarenal Capsules in Infectious Diseases.

The suprarenal capsules may be altered in the course of the most varied infections.

Capsular alterations are very frequent in syphilis (Virchow, Lancereaux, Chvostek) and especially in hereditary syphilis. Virchow and Huber noted fatty degeneration in them. Boerensprung, Ollivier and Ranvier described sclerosis of the capsules.

Since the classical memoir of Addison, tuberculosis of the suprarenal capsules has been described a great many times. There may also be cited cases in which the capsular lesions seem to have played the principal rôle in the genesis of morbid phenomena. In two patients who had rapidly died with typhoid symptoms Virchow found a hemorrhagic inflammation in the suprarenal capsules.

These facts indicate the interest attaching to the systematic study of the suprarenal capsules in infections. In their memoir on diphtheria Roux and Yersin state that the suprarenal capsules are intensely congested in guinea-pigs which had received living or sterilized cultures of Loeffler's bacillus. Charrin and Langlois made analogous statements regarding guinea-pigs inoculated with pyocyaneus virus and noted the presence of small, pigmentary granulations in the interior of the cells. In guinea-pigs which died twenty-four hours after inoculation with Friedlaender's bacillus the author found[1] the suprarenal capsules enlarged; instead of the fine yellow color they presented a dark, ecchymotic hue. In some instances they appear totally invaded by hemorrhages. On section the parenchyma appears transformed simply into a bloody mass; at the periphery of the organ only some intact parts are at times encountered.

[1] Roger. Les lésions des capsules surrénales dans les maladies infectieuses. La presse médicale, February 3, 1894.

Oppenheim and Loper studied[1] the suprarenal capsules of fifty-three men who had died from the most varied infections. They constantly found lesions, dilatation of the capillaries, diffuse or circumscribed hemorrhages, venous thromboses, cellular necroses, and, here and there, masses of polynuclears. These are substantially the same modifications as those observed in animals.

Considering the various results obtained and the frequent occurrence of sclerosis as a result of infectious lesions, we are led to the assumption that after an acute disease the suprarenal capsules often remain altered in a permanent manner; therefore, various disorders due to their incompetency may later be observed. As a matter of fact, since the clinical investigations of Sergent and Bernard we know that there is a syndrome different from Addison's disease, and characteristic of capsular insufficiency. In most cases the symptoms are connected with tuberculosis and follow an acute or subacute course, at times rapidly terminating in death. Of special importance for our subject is the fact that these phenomena at times develop on the occasion of even a slight infection, such as a pultaceous angina, as was the case observed by Sergent and Bernard.[2]

[1] Oppenheimer and Loper. Lésions des capsules surrénales dans quelques maladies infectieuses aigües. Société de biologie, July 13, 1901.

[2] Sergent and Bernard. Sur un syndrome clinique non addisonien lié a l'insuffisance capsulaire. Archives générales de médecine, July, 1899.

CHAPTER XIV.

INFLUENCE OF INFECTION UPON VARIOUS PARTS OF THE ORGANISM (*Continued*).

Disturbances and Alterations of the Nervous System. Cerebral Manifestations. Cephalalgia. Delirium. Relationship between Delirium and Lesions of the Liver and Kidney. Post-infectious Delirium. Tubercular Insanity. Obnubilation and Coma. Aphasia. Hemiplegia. Convulsions. Bulbar Manifestations. The Spinal Cord in Infections. Hydrophobia. Tetanus. Infectious Myelitis in Man. Acute Ascending Paralysis. Infantile Paralysis. Myelites in Various Infections. Diphtheritic Paralyses. Post-infectious Neuroses. Infectious Meningites. Cutaneous Manifestations of Infections. Exanthemata in the Eruptive Fevers. Mechanism and Variability of Infectious Erythemata. Relationship Between the Intensity of Eruption and Gravity of the Disease. Sudoral Secretion in Infections. Evolution of Exanthemata. The Muscular System in Infections. Infectious Osteopathies and Arthropathies.

The Nervous System in Infections.

All infectious diseases are capable of involving the nervous system; a few affect it in an exclusive or predominant manner.

For the convenience of description we may admit the following divisions:

1. Reactionary disturbances of the nervous system in the course of infections.
2. Non-specific lesions of the nervous system.
3. Awakening or appearance of nervous affections.
4. Specific lesions, viz., secondary localization of the infectious process.
5. Primary infection of the nervous system.

Nervous disturbances are observed in almost all diseases: fatigue, exhaustion, headache, delirium, convulsions, twitching of the tendons, and modifications in the activity of certain organs or systems are manifestations of frequent occurrence. They appear at a variable epoch of the evolution, subside with it, or persist after apparent cure of the disease. They may dominate the morbid tableau by reason of their intensity, thus leading to the development of particular clinical forms, such as ataxic, ataxo-adynamic, convulsive, delirious, and comatose.

The explanation of these disturbances is to be found, it seems, in intoxication.

It is, therefore, conceivable that causes favoring or aggravating the formation and retention of toxic substances play an important rôle in the production of the nervous phenomena. The lesions of the organs concerned in the transformation or elimination of the poisons, notably the liver, kidneys, and lungs, play an additional rôle, as do likewise the various conditions favorable to the production of toxins, the virulence of the microbe, rapid disassimilation, and hyperpyrexia. Thus, delirium may appear in consequence of lesions of an apparatus which until then was intact, for instance, the kidneys or lungs.

These ordinary reactions have a common basis. Although they are identical in all diseases, they at times present peculiar characters due to the action of specific products secreted by microbes and, more particularly, to the inherited or acquired predisposition of the subject.

It may be stated that, in a great number of cases, morbid manifestations represent functional reactions and simply express a disturbance of the nervous system; it is conceivable, however, that the prolongation or repetition of the derangement may result, more or less rapidly, in anatomical alterations. It is very difficult to say at what moment the functional disturbance gives way to anatomical lesion. It may even be doubted whether the distinction is well founded. In cells which no longer discharge their functions in a normal manner the protoplasm must certainly undergo alterations, although these changes are not appreciable until they become sufficiently well pronounced.

When the nervous affection becomes apparent during the course or at the end of the disease, the etiology is evident, but when months or years elapse between recovery from the first disease and the appearance of nervous phenomena, the problem then becomes highly complex; hence the origin and connection of the nervous symptoms have long been a matter of delicate discussion.

At the present day there can no longer be any doubt, since experimental pathology has succeeded in producing in animals a series of nervous affections, and notably myelitis, by means of inoculations with more or less virulent germs. Accurate clinical observation has finally removed the last shadow of doubt. It may now be affirmed that *all nervous affections*, save family and hereditary diseases, *are caused by some infection or intoxication.* The best differentiated

clinical types may follow the most varied infections. In the presence of this new pathogenic view we must not, however, lose sight of the rôle of predisposition, which alone enables us to explain the localizations of the process.

Infection may also provoke the appearance, aggravation, or return of latent, slight, or past manifestations. It is known that infection often acts as a provocative agent for certain neuropathies, particularly hysteria.

After the reactionary phenomena we may mention the secondary localizations of infectious processes. It suffices to cite, for instance, tubercles, abscesses, and gummata of the nerve centres and their envelopes. These lesions acquire no particular character from their localization. Pathogenic agents colonize in the nerve centres as they do in other parts of the organism, and there give rise to reactions.

Instead of being secondary, an infectious localization is at times primary. The pathogenic agent attacks the nervous system from the beginning. It may be propagated into the nerve centres or, having vegetated at some other point of the economy, secrete soluble substances which reach and become fixed in the nerve centres. As illustrations we may cite hydrophobia and tetanus.

These distinctions are of great theoretical importance. In practice, however, it is often difficult to determine the mechanism set in motion. It is therefore necessary, for the description of facts, to consider them from the clinical standpoint and simply pass in review the manifestations which may occur in the various parts of the nervous system, namely, the brain, the medulla oblongata, the spinal cord, and the peripheral nerves.

Cerebral Manifestations. The influence of infectious diseases upon the brain may be expressed by two orders of phenomena: (1) diffuse manifestations, such as headache, incapacity for work, cerebral obnubilation, delirium, and convulsions; (2) symptoms indicating focal lesions, such as aphasia and hemiplegia.

The necropsy sometimes reveals a focus of softening due to an embolus or thrombus; at other times, acute encephalitis, a cerebral abscess, a meningitis, or a thrombosis in the sinuses. Such marked lesions are seldom met with. In the great majority of cases there is found simply a congestion and, at times, slight hemorrhage. In some instances a slight serous effusion is detected in the meshes of the pia mater and in the ventricles. Lesions of this kind are encountered, especially in typhoid fever. In this disease more profound

alterations are sometimes met with, such as arteritis, meningeal hemorrhages, and cerebral abscesses.

A last group comprises those cases in which the necropsy is negative: the brain appears healthy. In such cases the cerebral symptoms have been attributed to circulatory disorders, pyrexia, and microbic localizations. It is now known that the question is one of intoxication of the organism by microbic products and by waste of cellular nutrition. It is, therefore, perfectly intelligible that results should greatly vary according to the nature, intensity, or duration of the infectious process.

Cephalalgia. Cephalalgia is observed in all febrile processes; it assumes a certain importance in several diseases. It is particularly interesting to study headache in typhoid fever. It often constitutes the first symptom of the disease. A persistent headache accompanied by some gastric disturbances, occurring in a young person who has been a short time in a great city, should immediately suggest typhoid fever. During the stationary stage headache persists; it is generally very severe, and the patient refers his insomnia to it. In cases of moderate intensity, headache lasts to the end of the evolution; in graver cases it disappears, overcome by the stupor which invades the patient. When the question is one of those slight forms designated as "walking typhoid cases" headache is often the only symptom, and thus acquires great diagnostic value.

Cephalalgia is less marked in the eruptive fevers. Measles is attended by hardly any headache, and the slight pain seems to be referable to the coryza. It is more intense in variola and scarlet fever, but generally ceases with the appearance of the eruption. The return of headache during convalescence is often the first sign of a renal complication.

We must also note the importance of headache in various forms of malaria. It is often one of the first morbid phenomena. Its appearance in a man who has just passed through a swampy country should immediately suggest malarial infection. It is one of the best premonitory symptoms. It is also one of the first symptoms of the intermittent paroxysm; cephalalgia precedes the chills, persists during the cold stage, and diminishes during the stage of heat. When it occurs in the intervals of paroxysms the development of a pernicious character is to be feared. Finally, after cure of the febrile paroxysms, headache may recur in a regular manner; it then represents a form of masked malaria which is not rare in Europe.

At times headache indicates a cerebral complication; it may mean involvement of the meninges, especially in those cases in which a suppurative lesion of the nose or ear exists. It is well to note that, contrary to classical opinion, meningites, even of suppurative type, are often latent, and give rise to no reaction and, notably, to no pain.

Besides headache, the patient not infrequently complains of *vertigo*. This symptom is especially marked in influenza and typhoid fever. In the latter disease it is manifested as soon as the patient changes position or sits up in bed. At the beginning of the infection, when the diagnosis is yet doubtful, this phenomenon possesses certain semiological value.

Delirium. The frequency and clinical appearance of delirium depend upon two factors: the state of the subject and the nature of infection.

The age of the patient plays a very important rôle. Children are often subject to delirium, except, of course, in the first years of life, when the cerebral centres are not sufficiently developed for reacting. The newly-born is a medullary being, and the infectious manifestations are the result of the action upon the spinal cord. Delirium is of very frequent occurrence in adults; it is less frequent in the aged; the latter are more apt to be attacked by torpor and adynamia. While more common in debilitated or overworked persons, and in women more than in men, delirium is particularly influenced by hereditary or personal antecedents of the patient. Certain individuals predisposed by heredity become delirious on the occasion of any febrile process; it is a mild form, and ceases as soon as the attention of the sufferer is fixed. Acquired predisposition is generally due to previous affections, mainly to intoxications. Alcoholism plays the principal rôle and gives rise to well-known special disturbances described under the name *delirium tremens*. This is an event occurring in the course of a chronic intoxication and as a result of an abrupt shock. It, therefore, generally appears in diseases characterized by a sudden onset, such as variola, scarlatina, erysipelas, rheumatism and, above all, in pneumonia. It is exceptional in those infections which, like typhoid fever, set in slowly and progressively.

From a general standpoint, delirium is manifested in three different degrees: 1. Mild delirium, generally bearing upon the habitual occupations of the patient and ceases when his attention is called to it. 2. Delirium characterized by the muttering of incoherent speech, and often accompanied by sensory hyperesthesia, which explains the hal-

lucinations and illusions of sight and of hearing. 3. Furious delirium is one of action: the patient howls, sings, recognizes nobody, answers no questions. Sensibility is diminished. The sufferer is detached from the external objective world, and is seized with terrifying hallucinations. With haggard and congested eyes and trembling limbs he leaves his bed and runs about the room, fighting those who try to arrest or calm him.

The delirious manifestations of the stationary period generally disappear at the end of the disease. In certain instances, however, some trouble of the intellect or memory may persist. In other cases more serious phenomena appear. Such, for example, is the condition described by alienists under the name *mental confusion*. It occurs in the most varied diseases: in typhoid fever, variola, cholera, influenza, pneumonia, and erysipelas. The ideas of the victim are so confused that he utters only fragments of phrases; his language becomes unintelligible. His perceptions are not clear. His face is weak and stupid. In spite of their apparent gravity, however, these troubles are in most cases transitory, and gradually disappear.

Post-infectious Delirium. Mania may occur in consequence of the most varied infections: typhoid fever, rheumatism, erysipelas, eruptive fevers, cholera, etc. On consulting a treatise on mental pathology it will be seen that the most varied clinical types of mental diseases may occur as a result of an infection. The same diseases are mentioned in the etiology of manias, mental degenerations, various forms of insanity, and even of general paralysis. Their relative frequency is not exactly the same. Thus, mental degenerations, accompanied or unattended by bodily degenerations, are the inflictions of hereditary syphilis; they are also observed after typhoid fever, but are exceptional after other infections, such as the eruptive fevers, diphtheria, mumps, and whooping-cough. In the etiology of general paralysis (aside from the influence of syphilis, which will be referred to later) are cited typhoid fever, influenza, pneumonia, diphtheria, variola, and especially erysipelas.

Tubercular Insanity. Although insanity is at times consecutive to a transitory disease, it may also occur in the course of a chronic infection, such as syphilis or tuberculosis. The relationship between insanity and phthisis has been repeatedly studied. Alienists have long noted the frequent coincidence of the two processes, the frequency of tuberculosis among the ancestors of the insane, and at

times the alternation of thoracic symptoms and of cerebral disorders in the same individual.

The mental state of the tubercular is often very peculiar. Their optimism and indifference is a matter of common observation. Some of them recognize their state and accept it with resignation. How different is this from the alarm into which most people are thrown on the slightest morbid manifestation. Certain tubercular subjects, however, are of a different temper; they always complain, and nothing satisfies them. Others become suspicious, and may believe themselves to be objects of persecution.

Finally, at the terminal period, intellectual derangements appear, as a rule. They occur tardily, however; a violent delirium with hallucination is a symptom of approaching death.

In certain cases a paroxysm of true insanity may occur in the course of ordinary tuberculosis. We had the opportunity to observe a case of this kind in which very marked disorders evolved in successive periods, characterized by alternating manifestations of depression and excitation.

Role of Infections in the Development of General Paralysis. Among the maladies of infectious origin, general paralysis deserves first mention. It follows typhoid fever, pneumonia, diphtheria, variola, and, as has been shown by Bayle and Baillarger, especially erysipelas. The influence of syphilis seems also to be undeniable. Syphilitic general pseudoparalysis, however, must be distinguished from true general paralysis. The former is connected with diffuse syphilitic lesions and is remarkable for the existence of certain peculiar symptoms—*i. e.*, ptosis, strabismus, local paralyses, and cephalalgia. Delirium is slight and often assumes the circular form. Finally, its course is different; it is often regressive, and a cure may be effected by specific treatment. Aside from this somewhat peculiar clinical type it must be recognized that syphilis is too frequently found in the antecedents of general paralytics to be simply an accidental coincidence. Syphilis does not, however, produce general paralysis; it fulfils here the same rôle as in the development of locomotor ataxia: it is an auxiliary cause acting upon predisposed individuals.

Obnubilation and Coma. Infections often give rise to an obnubilation sufficiently pronounced to border on coma. It is a nervous depression supervening at once or following phenomena of excitation, notably delirium.

Cerebral obnubilation is very marked in typhoid fever, typhus, and pneumonia in the aged. It also characterizes one of the forms of pernicious malarial fever. In the course of the eruptive fevers it presents a certain diagnostic value according to the date of its appearance. At the beginning of scarlatina and measles a semicomatose state is not a symptom of extreme gravity, at least in children. If, however, it does not subside at the time of eruption the prognosis becomes grave.

The appearance of coma during convalescence indicates a complication and particularly a bronchopneumonia in a case of measles, and a nephritis in a case of scarlatina.

These comatose manifestations are at all events rare. With their study we have completed the consideration of diffuse cerebral manifestations. We shall now review certain phenomena which seem to indicate a more precise localization.

Aphasia. Aphasia may occur unassociated with hemiplegia. It appears during convalescence from the eruptive fevers, erysipelas, and particularly typhoid fever. It is most frequently observed in children. At any rate, the trouble is incomplete and transitory, and recovery is effected in two or three weeks. Leyden attributes it to a focus of slight encephalitis. Certain cases might perhaps be explained by neurotic disorders, as we are led to believe by observation of a case of measles in a girl, three years of age, who, two days after the fall of the fever, had frequent fits of hysteria, and at the same time lost the use of language, save two words, "Boni, madame," which was her invariable reply to all questions. This aphasia lasted fifteen days and then gradually disappeared.

We must not overlook aphasia occurring in malaria. In some cases the disturbance of speech appears after a regular paroxysm; it is transitory and not serious. At times it manifests itself in a pernicious paroxysm and is of grave prognostic significance.

Hemiplegia. Hemiplegia may be produced by various mechanisms. It may be due to emboli derived from a clot of phlebitis or vegetations of an ulcerative endocarditis. In the latter instance the symptom acquires a certain diagnostic value. When the diagnosis is doubtful as to the nature of infection observed—when, for example, typhoid fever is thought of—the sudden appearance of hemiplegia will lead to a more careful examination of the heart, and thus enable the physician to recognize the nature of the events.

Hemiplegia dependent upon a focus of cerebral arteritis is an

incident of rare occurrence. We have observed a case of this kind, that of a man, thirty-three years of age, who, consecutively to a gastroenteritis, developed a right hemiplegia involving the limbs and the face, but sparing the orbicularis palpebræ. The necropsy revealed an acute arteritis in the arch of the aorta and red softening occupying the middle of the ascending convolutions on each side of Rolando's fissure, affecting quite deeply the cortical part.

Hemiplegia is not extremely rare in pneumonia, at least in the aged. It sets in after an apoplectic attack and is often attended by conjugate deviation of the head and the eyes. Death occurs within a few days in coma. At the necropsy cerebral softening is discovered. According to Straus, this lesion is constant, but so small as to easily escape notice.

There are also transitory hemiplegias observed, particularly during convalescence from infections, but they are extremely rare.

Convulsions. As infantile poliencephalitis is less frequent than poliomyelitis, owing to the fact that in children the brain is less active than the spinal cord, the same is true of delirium which, in children, is replaced by convulsions, especially in those predisposed by heredity or innateness. When they occur at the beginning of infections they are not of grave diagnostic significance. They often accompany the invasion of an eruptive fever, angina, and notably pneumonia. In the last-named disease convulsions are observed chiefly in children under two years of age, thus justifying the assumption of an eclamptic form.

Tardy convulsions, unlike early ones, frequently announce the development of some complication. In measles they must suggest bronchopneumonia; during convalescence from scarlatina they generally constitute the first symptom of nephritis. In other instances they express some lesion of the nervous centres, and are, for example, related to the development of meningitis. If convulsions occur in the course of a whooping-cough, without aggravation in the general state of the patient and without production of fever, they are to be attributed to an exaggeration of the nervous reactions induced by the disease: the local convulsion is generalized. On the other hand, if at the same time there is persistent dyspnea and a rise in temperature, the patient must be examined with greater care, and almost always bronchopneumonia will be discovered.

Finally, as the majority of adults succumb in delirium, so most children under two years of age die during terminal convulsions.

They behave at the end of infection as they do at the beginning, presenting nervous reactions which are referable to the same cause as in adults, but are localized in different parts of the nervous system.

Convulsions are quite uncommon in adults. Scarlatinal nephritis, which produces convulsive uremia in children, gives rise to dyspneic, delirious, or comatose uremia in adults. Puerperal eclampsia is an exception to this rule; still, in not a few cases puerperal uremia is expressed by other manifestations, notably by a violent delirium which, in the absence of an examination of the urine, would very likely be mistaken for a phenomenon of acute insanity.

Bulbar Manifestations of Infections.

The majority of infections affect the bulbar centres. Fevers seem to be dependent upon dynamic modifications produced in the medulla oblongata. Certain phenomena accompanying fever, notably chills, are also referable to a bulbar influence.

The medulla oblongata also contains centres governing the functions of the principal organs. Various cardiac disturbances are of bulbar origin. Acceleration of pulse in fever is not simply due to the rise in temperature, for, if such were the case, it would follow nearly the same course in all diseases. The fact is, however, that certain diseases affect far more than others the number of pulsations and are precisely those maladies which most easily excite nervous reactions. In this respect scarlatina is the leading affection. In this disease, for the same degree of temperature, the pulse is far more rapid than in other infections. This is even a valuable diagnostic symptom, since it enables the physician to state, prior to the eruption, that the sore throat is probably of scarlatinal nature. On the other hand, slowness of pulse may express the influence of an infection upon the bulb, and such slowness, coinciding with the thermal elevation, becomes a striking feature. In a man, twenty-one years of age, suffering from a serious scarlatina complicated with albuminuria, the number of pulsations fell to 52, although the temperature was 102.2° F. (39° C.). This state persisted for three days. It was probably due to a bulbar disorder, since, under the influence of a small dose of atropine, which diminished the action of the pneumogastric nerves without suppressing it, the pulse-rate rose to 64.

We likewise attribute to disturbances of cardiac and respiratory centres the arrhythmias, the irregularities of the heart's action, which

occur without the slightest demonstrable lesion in the myocardium. A similar explanation must be admitted with reference to certain paroxysms of dyspnea, acceleration or retardation in respiratory movements, which are accounted for neither by fever nor the state of the heart, kidneys, or lungs.

The Spinal Cord in Infections.

The participation of the spinal cord in infectious processes is demonstrated beyond dispute by the study of two diseases: one caused by multiplication of the pathogenic agent, the other by the action of microbic toxin—we refer to hydrophobia and tetanus. In hydrophobia the pathogenic agent acts by means of the products which it secretes. When, after having been freed from all figurate elements, an emulsion of the spinal cord of hydrophobic animals is injected into dogs, paralytic phenomena are produced. It is an intoxication, not an infection, since the cord of these inoculated dogs is not virulent.

This toxin is produced in the various parts of the nerve centres, and these are invaded successively, not simultaneously. The pathogenic agent slowly propagates and colonizes. The experiments of Di Vestea and Zagari show that the introduction of the virus into the sciatic nerve causes a more marked paralysis on the side into which the inoculation is made, and that the tail of the horse becomes virulent before the medulla oblongata. Clinical observation is in harmony with these experimental facts; it shows that convulsive or paralytic phenomena are often more pronounced on the bitten side. According to the remark of the authors above mentioned, a bite in the lower extremities commonly gives rise to paraplegia, while the rabid forms usually occur when the initial lesion is inflicted on the head or upper extremities.

Of the two clinical forms of hydrophobia, one, the rabid form, is in fact characterized by the predominance of cerebral manifestations; the other, the dumb or paralytic type, by the prevalence of spinal phenomena. These two forms may be encountered in all animals, but their relative frequency varies from one species to another. The rabid form is more frequent in the dog, while in the rabbit the disease almost constantly assumes the paralytic form.

Anatomical pathology shows, on the other hand, that the lumbar spine is affected if the person is bitten in the lower extremities; if the wound is received in the upper extremities the cervical spine is

found to be the seat of alterations, these alterations consisting not in mere congestion, but in small foci of softening. Microscopic or even larger hemorrhages resulting from the rupture of congested capillaries as well as thrombosis are lesions of frequent occurrence. The nerve cells are altered; at some points they are destroyed and replaced by masses of embryonal elements or neuroglia tissue.

In view of the results furnished by experimentation and clinical observation we may state, in conclusion, that the agent of hydrophobia is essentially a parasite of the nervous system, the peripheral prolongations of which it follows in order to reach and localize itself in the nerve centres and there produce its toxin. According to the ancient expression of Romberg, hydrophobia may therefore be said to be a toxoneurosis; we must only add: an infectious and specific toxoneurosis.

Tetanus. The second infectious toxoneurosis known is tetanus. It essentially differs from the preceding infection in that the pathogenic agent remains localized at the point of introduction and secretes toxins which follow the nerves in order to reach the spinal cord, the bulb, and the brain. Its mode of action has been and is still a matter of discussion. Courmont and Doyon believe its action to be that of a ferment which gives rise to a new poison of a convulsifying character. Others, following Ehrlich, admit a combination of the toxin with the protoplasm of the nerve cells, an intracellular transformation thus being effected.

It remains to determine what part of the nervous system is the starting point of the disorders. Pathological anatomy having afforded no conclusive results, physiological analysis must be resorted to. At present there is general agreement for localizing the disorder in the cord and the medulla oblongata; and, following Courmont and Doyon,[1] it is admitted that the process is one of exaggerated sensitiveness of the reflex axis, the poison acting probably upon the sensory neuron. This conclusion is in perfect harmony with the results of experiments made by the author as regards the sensitiveness of tetanic animals to the action of strychnine.[2]

Guinea-pigs, from two to seven days after inoculation with tetanic toxin, received beneath the skin small doses (from 0.5 to 1 mg.) of strychnine sulphate. They presented convulsions and, in most

[1] Courmont and Doyon. Le tétanos. Actualités médicales, 1899, vol. i.

[2] Roger. Action de la strychnine et du chloral sur les animaux tétaniques. Soc. de biologie, May 20, 1899.

cases, soon succumbed. Control guinea-pigs withstood the same amounts of the alkaloid without presenting the slightest disturbance.

Infectious Myelites in Man. Numerous facts of comparative and experimental pathology demonstrate the frequency of paralyses of spinal origin consecutive to infections. In clinical experience it is often difficult to determine a localization. The symptoms may depend upon very different processes. Three diseases or rather three clinical types may be referred to infection. These are the acute ascending paralysis, infantile paralysis, and acute spinal paralysis of the adult. Their history will complete the teachings already furnished by the study of hydrophobia and will enable us to better appreciate the complex facts to be later described.

Acute Ascending Paralysis. Acute ascending paralysis or Landry's disease may occur in typhoid fever (Landry, Leudet, Pitres, and Vaillard), pneumonia (Gubler and Landry, Macario), measles (Barlow, Negue), variola (Gubler, Bernhardt, Gross, Chalvet, Oettinger, and Marinesco), in consequence of puerperal septicemia (Landry) or urinal septicemia (Orcel and Stourine, Prince), and consecutive to suppurative wounds produced by a vesicatory (Landry, Gubler). In some cases the invasion is announced by certain disturbances attributed to influenza or an attack of indigestion. In other instances the onset is characterized by general manifestations, malaise, loss of appetite, chills, and especially fever. Finally, as in all microbic processes, the intervention of some auxiliary cause is often noted in the beginning of the disease, such as indigestion, cold, overexertion, and excesses, which favor the development and localization of the germs.

Some of the symptoms of the stationary period indicate the infectious nature of the malady. First of all, fever which, it must be acknowledged, is not constant; also malaise, anorexia, and, not infrequently, hypertrophy of the spleen. What further strengthens the conviction that acute ascending paralysis must be of infectious origin is the fact that there is an infection of the nervous centres which, by its symptoms and evolution, strongly resembles Landry's paralysis —reference is here made to paralytic hydrophobia. The perusal of certain observations leads to the question whether some cases recorded as examples of Landry's paralysis are not due to the virus of hydrophobia. Leaving aside this doubtful question, it is noticed that the evolutive analogy leads to the assumption of a pathogenic analogy and, therefore, to a search for an animate agent in Landry's

disease. Researches in this direction have already been pursued with some success. Baumgarten found in the blood and organs a bacillus resembling that of anthrax. Marie and Marinesco obtained a similar result. Centanni saw numerous microbes ranged in a semilunar form around the fibres of peripheral nerves, none being encountered in the cord. It is impossible, however, to express a decided opinion with regard to these various findings, since none of the foregoing authors completed his investigations by cultivation and inoculations.

In a case of Curschmann the symptoms made their appearance in the course of a typhoid fever and were ascribed to Eberth's bacillus, which was, in fact, found in the white substance of the spinal cord. The nature of the microbe was determined by cultivation and inoculation. In other instances common or at least non-specific bacteria have been encountered. The staphylococcus aureus was found twice by Eisenlohr, the streptococcus in the case of Oettinger and Marinesco, which coccus was cultivated in the case of Remlinger. Lastly, in a case in which microscopic examination had failed to disclose the presence of any germs, Thomas obtained a culture of a micrococcus liquefying gelatin.

Thus in nine cases which have been more or less carefully studied from a bacteriological standpoint there was found twice a bacillus resembling that of anthrax, twice undetermined microbes, once Eberth's bacillus, twice the staphylococcus aureus, and twice the streptococcus. In two other cases, one observed by Eisenlohr, the other by Albu, the research for bacteria was negative.

From these somewhat dissimilar facts no definite conclusion can be derived. It can only be stated that the majority of modern observations lead to the assumption that Landry's disease is an acute poliomyelitis which may be produced by the most varied microbes.

The following observation[1] tends to support this view: A man, thirty-three years of age, ten days before his admission to our hospital experienced sensations of intense cold in the lower extremities, and, three days later, numbness in the legs, but no pain at any time. The lower extremities became progressively weaker, and he was compelled to lie in bed; then throat symptoms appeared, upon which he was sent to the hospital. He suffered a violent paroxysm of dyspnea on taking a glass of milk. His intellect was intact. Perspired pro-

[1] Roger and Josué. Un cas de paralysie ascendante aiguë. La Presse médicale, July 27, 1898.

fusely. He was hoarse, but nothing abnormal was found in the throat. Every time he drank, however, he had a paroxysm of suffocation. Paralysis of the lower extremities was complete; the upper extremities were only weakened. There was also slight anæsthesia, which was more marked in the lower than in the upper extremities. The patellar reflexes were abolished as well as the tendon reflexes of the upper extremities. Pulse 112; temperature 101.6° F. (38.7° C.) in the morning, 100° F. (37.8° C.) in the evening. On auscultation sibilant and sonorous râles were heard. He died in the night during an attack of dyspnea. The histological examination of sections of the lumbar enlargement showed lesions in the cells of the anterior horns, remarkable alike for their degree, amounting to an atrophy of the nervous elements, and for their diffusion: nearly all the cells were altered. On bacteriological examination no microbic foci were found. We therefore resorted to cultivation and inoculation in order to determine the cause of the disease.

With a sample of the blood which was taken from the right heart immediately after death we obtained cultures of a microbe presenting all the characters of the pneumococcus. With these cultures we made inoculations into animals. Rabbits presented paresis or spasmodic paralysis in the hind legs. Their blood, cultivated in various media, yielded pure cultures of the pneumococcus.

Our observation is the first to establish the existence of an acute ascending paralysis produced by the pneumococcus. This result is not to be wondered at. There are cases on record showing that pneumonia may be followed by an ascending paralysis. Landry's famous observation is an illustration thereof: the patient had had an attack of pneumonia from which he had not completely recovered. He remained in that condition for two months, and then developed paralysis, which killed him in a week. It may, of course, be objected that, in this case, the lapse of a long period of time between the thoracic and spinal manifestations renders impossible the unreserved admission of a relationship of cause and effect.

No such objections can be raised against our case, which demonstrates the possibility of an ascending paralysis of pneumococcic origin. It is true that in our case the nature of the infection could not be determined without the assistance of bacteriology. The lungs did not present the lesions which the pneumococcus usually produces therein. It is well known to-day, however, that the pneumococcus is capable of giving rise to various infections without pulmonary

alterations. Numerous facts have been related to show that this microbe frequently reaches the nervous centres. It is not strange, therefore, that it may also produce spinal localizations.

The pneumococcus isolated by us possessed the property of producing in animals, as it had done in man, nervous manifestations. Three of our rabbits developed paraplegia under its influence. It seems, therefore, that after it had once given rise to spinal disorders the microbe had acquired a sort of elective harmfulness for the nervous system. A study of this fact led us to the view that microbes may become accustomed to a residence in certain parts of the organism, and thus always manifest a tendency to localize themselves in the same tissue in a predominant or exclusive manner (p. 101).

Infantile Paralysis. The infectious nature of infantile paralysis is established upon a fairly large number of clinical proofs. The spinal symptoms have at times developed consecutively to a well-determined infection; at other times they have been observed simultaneously in a number of children, and prevailed in an epidemic form (observations of Cordier, Leegaard, Medin, Briegleb, Cerversato, Auerback, Zappert). These epidemics are commonly observed during summer, and often coexist with epidemics of polioencephalitis. The symptoms develop at once or in consequence of some infection, such as measles, scarlatina, or erysipelas. It is not an easy matter to say whether acute myelites should be related to cerebrospinal meningitis and considered as due to a specific microbe, or whether they are caused by ordinary bacteria the pathogenic rôle of which has been demonstrated by experimentation.

The same reflections are applicable to the acute spinal paralysis of adults, the symptoms and course of which recall exactly those of infantile paralysis and which may also prevail in epidemic form. In the report given by Leegaard fifty-four individuals were affected. The greatest number of cases are observed, on the one hand, under four years of age, and, on the other, between fifteen and nineteen years; a few patients, however, were above thirty. Of the fifty-four persons attacked, twelve recovered completely; thirty retained some paralysis; ten remained impotent, and two died.

Myelites in Various Infections. Myelites which develop in the course or in consequence of infectious diseases may be divided into two groups according as they are diffuse or systematic.

Diffuse myelites are very frequent, but they may at times be so slight as not to be revealed by any symptom. Widal and Bezançon

have found, for example, alterations in the cells of the anterior horns in two variolar patients who, during life, had not presented any spinal symptom. One is thus led to ask whether certain motor difficulties experienced by convalescents and attributed to asthenia do not depend upon superficial and curable lesions of the spinal cord.

In certain instances myelitis appears at the beginning of an infection. Such is particularly the case in variola. The intense backache of which patients complain indicates the early participation of the spinal cord in the process. There may be nothing more than congestion. It is known, moreover, that backache occurs at the onset of other eruptive fevers. In fact, all the infectious diseases might be cited in this connection. Typhoid fever, influenza, pneumonia, erysipelas, dysentery, and gonorrhea are among the most frequent. Diphtheria might be added, although authorities are greatly inclined to-day to refer the paralyses of this disease to peripheral neuritis.

The symptomatology is extremely variable. In some instances disorders rapidly develop, as in acute ascending paralysis; in other cases the manifestations are at first diffuse, but subsequently become localized in a certain part of the spine. At times the victim is paralyzed in the lower extremities or only in a limited part of the body. In the presence of these various paralyses the question arises as to whether they are due to real medullary lesions or to neuritis, neurosis, or hysteria. The question often remains unanswered.

There can be no doubt in the case of a well-determined disease, such as tabes dorsalis. The rôle of infection in the genesis of this myelitis is incontestable. Numerous statistics show that nearly all sufferers from tabes have a syphilitic history. This fact, however, does not warrant the conclusion that locomotor ataxia is a syphilitic disease, since it does not respond to the specific treatment, and at the necropsy no lesion is found presenting the characteristics of syphilis. In nine out of ten cases of tabes syphilis is said to be found in the antecedents. Granted. The tenth case, however, is sufficient to prevent tabes from being held as a syphilitic disease. Syphilis does act, but only as an auxiliary cause. Other causes could, however, play the same rôle, and this is proved to be true by the fact that a great number of infections, such as pneumonia, typhoid fever, cholera, variola, etc., are often found in the antecedents of non-syphilitic sufferers from tabes.

We must likewise note that progressive muscular atrophy ensues

sometimes after infections such as typhoid fever, measles, rheumatism, cholera, and pneumonia.

Lastly, Desnos and Babinski have shown syphilis among the causes of syringomyelitis. This affection has sometimes followed typhoid fever, rheumatism, pneumonia, gonorrhea, or even a simple bronchitis.

Infectious Neurites.

The participation of the peripheral nervous system in infectious processes is evidenced by the frequency of neuralgias, notably facial, sciatic, and intercostal neuralgias. Acute as well as chronic infections often give rise to these nervous manifestations. They have been observed as a result of influenza and pneumonia. I have met with several examples consecutive to scarlatina and erysipelas. Their frequency in malaria and syphilis is well known. In all cases of rebellious sciatic neuralgia the cause of which cannot be determined, Landouzy advises a search for tubercular manifestations.

Herpes zoster sometimes develops in consequence of an infection, notably erysipelas and scarlatina. The frequency of primary herpes in certain seasons, the febrile movement accompanying it, and the immunity conferred by a first attack seem to give a solid basis to the opinion that this eruption depends upon an infection of the nervous system.

The motor disorders caused by peripheral neuritis must be carefully studied. They are often contrasted with similar disturbances produced by medullary lesions, and some authorities have attempted to establish differential characters between myelitis and neuritis. It is, perhaps, an error to separate too widely the two processes. The peripheral alterations possibly depend upon some central lesion, though the latter may be slight and easily escape notice, or be inappreciable by our present means of investigation.

Infectious polyneurites are often divided into two groups, according as they occur in the course of a definite disease or independently.

Secondary infectious polyneurites are observed in connection with all acute infections. They at times appear in the course of chronic infections, such as paludism, tuberculosis, syphilis, and leprosy. It is known that in the last-named disease the bacilli become localized in the nerves and there produce small nodules.

Primary polyneurites may be acute or chronic. In the former case they constitute a clinical type described by Leyden; in the

latter instance it is a malady of hot countries: beriberi. Balz and Scheube found in the affected nerves a diplococcus, cultures of which gave rise to peripheral neuritis when inoculated into dogs and rabbits.

Acute infectious polyneurites sometimes occur in epidemic form, as Eisenlohr has observed the disease in Hamburg. They often begin suddenly by intense pain in the extremities, notably in the lower, and are attended by fever, at times delirium, insomnia, and a certain degree of stupor. There is albumin in the urine, and the skin may present a subichteric aspect.

Then paralysis, accompanied with shooting pains, supervenes. Later, sensation is diminished, and may sometimes advance to anesthesia, especially at the periphery of the limbs. The paralysis is of the flaccid kind, without contracture, and attacks the lower extremities, although in some cases it may assume an ascending course and also involve the upper extremities. The muscles soon become atrophied, while fat accumulates in the subcutaneous cellular tissue. Tendon reflexes are diminished or abolished. Electric contractility of the muscles is generally diminished, the reaction of degeneration is often observed. In cases in which the pneumogastric is involved, death may ensue by asphyxia at the end of a period varying from six days to a month. In other cases the process is arrested and subsides; the patient recovers completely or else retains some paralyses.

Pseudotabetic polyneurites are readily distinguished from locomotor ataxia by the gait of the patient, the legs being lifted high instead of groping, by the absence of visceral disturbances, and by favorable evolution of the lesions.

Pseudotabes has been observed in consequence of a great number of infectious diseases, and notably after diphtheria and erysipelas. As, however, these two diseases are most frequently attended by paralytic manifestations of all descriptions, it is interesting, to devote a special study to them.

Diphtheritic Paralyses. In my personal statistics I find in a total of 216 cases of diphtheria in adults 42 attacked by paralysis. In 39 of these the palate was paralyzed, in 12 the extremities were also involved. In nearly half of the cases paralysis appeared two to fifteen days, exceptionally three to four weeks, after the beginning of the disease.

Motor disturbances may be accompanied by disorders of sensation

and of the senses. One patient lost taste, so that sugar, salt, and quinine sulphate, when applied to the tongue, had a slightly sugary taste to him.

Trousseau has laid stress, though with manifest exaggeration, upon the wandering character of diphtheritic paralyses. In fact, one is at times astonished at modifications occurring suddenly. A patient under my observation suffering from post-diphtheritic pseudotabes was almost incapable of walking. A fire occurred in the ward where he was lying, and soon it was so full of smoke that those who ran to rescue him were forced to fall back. Another attempt was about to be made when the patient was seen coming out quietly. Under the influence of the emotion, paralysis had suddenly vanished, and recovery proved to be permanent.

Fatal termination results from the entrance of food into the respiratory tract. This accident is particularly frequent when the glottal muscles are paralyzed coincidently with the palate. The result is a bronchopneumonia or a pulmonary gangrene, invariably terminating in death. Death occurs by asphyxia, at times by syncope.

It is to be noted that the employment of the esophageal bougie, far from preventing the passage of food into the respiratory tract, seems to favor this accident; the fluids introduced into the stomach are soon rejected by regurgitation, and enter the trachea. I have seen two patients succumb in this manner.

In certain cases death results from an unexpected attack of syncope. A man, twenty-five years of age, who had paralysis of the palate, died suddenly twenty-four hours after the beginning of the disease. Histological examination demonstrated the integrity of the bulbar centres and pneumogastrics, but revealed a diffuse myocarditis, which had probably played the principal rôle.

There is at present an inclination to believe that diphtheritic angina is the only kind of sore-throat capable of giving rise to paralyses. Some of my observations show this opinion to be exaggerated. A woman, of twenty-five years of age, who had recovered from a phlegmon of the tonsil, retained a paralysis of the palate; the fluids flowed through the nose, and the patient was forced to incline the head backward in order to swallow. This paralysis disappeared suddenly four days later. In face of this sudden termination one may think of a hysterical phenomenon; no stigmata of this neurosis were found, however.

Erysipelous Paralyses. Next to diphtheria erysipelas is, perhaps, the disease which most frequently gives rise to paralytic disturbances. My former interne, Dr. Crochet, made an excellent study of it in his thesis (1895).

Trousseau observed impotence of the dorsolumbar muscles consecutively to diphtheria, rendering vertical position impossible. I observed a young girl of sixteen years, convalescent from a severe erysipelas, who was incapable of sitting up in her bed or raising her head. On the following day she was able to get up and walk when supported, but she had a tabetic gait. There was also a persistent paralysis in the nape of the neck. The phenomena were gradually ameliorated, and the patient recovered in a fortnight.

I have noticed the appearance of painful spasms and marked impotence in the lower extremities in two convalescents from erysipelas. One of them, a woman of twenty-one years, without any nervous antecedents, suffered from shooting pains in the legs after an erysipelas of moderate intensity. She could not stand on her feet for more than five minutes at a time; when she rose, her legs remained in a position of semiflexion, and her head fell upon her chest. At the end of a month all these symptoms were almost completely cured.

In some cases peripheral paralyses occur. A manifestation of frequent occurrence consists in a combination of paralysis of the lower extremities and cutaneous hyperesthesia and exaggerated reflexes. In some instances the upper extremities are also involved. Paralysis of accommodation preventing vision at close range, facial paralysis, amblyopia, and diminution in auditory acuteness are likewise among the possible events.

Scarlatinal Paralyses. Of all the eruptive fevers, scarlatina is the most often productive of paralytic disturbances; still, these are rare. In a total of 2213 cases I found only four cases of incomplete paraplegia. In one of these instances, a man, who suffered from scarlatinal angina, developed paralysis of the palate on the second day. Three days later the lower extremities were slightly involved; next the right arm was attacked; movement was still possible, but difficult and maladroit. These symptoms disappeared in ten days. In the antecedents of this man was found the occurrence of a transitory paralysis occurring four years previously as a result of some work done in compressed air.

Post-infectious Neuroses.

The influence of infection as an occasional cause of neuroses is at present well known. In most cases the disorders are of a hysterical character. In a man convalescent from scarlatina attacks of convulsions occurred. In another, anesthesia of general sensation and of the senses developed after erysipelas. In still other cases, trembling is observed; such was the case in a man, sixty-nine years of age,[1] whose trembling was first mistaken as paralysis agitans. The rhythmical oscillations of the forearms were repeated 140 to 150 times a minute. When, however, he attempted to carry a glass of water to his mouth the trembling changed its character; instead of ceasing during the movement, as is the case in paralysis agitans, the range of the oscillations was exaggerated, so that the water was thrown out and the patient struck his face. The patellar reflexes, on the other hand, were diminished. The uncertain diagnosis was singularly facilitated by the study of his antecedents. He belonged to a family of nervous people. His father, of a violent temper, had committed suicide at the age of eighty-six years, because he had become incapable of riding a horse. One of his sisters has attacks of hysteria. During his long life he had been sick only twice; he had two attacks of pneumonia, and here is the curious series of accidents which were produced by these infections:

His first attack of pneumonia occurred in 1860, at the age of thirty-five years. While being treated under Bouillaud he was subjected to blood-letting fourteen times in five days. In spite of such treatment, the patient was too agitated, and therefore he was isolated. This measure irritated him; he was furious and, for the first time in his life, he had a nervous paroxysm, fought, cried, and all ended in profuse sweating; he then fell into a sound sleep. On awakening the following day he noticed that he could not move his lower extremities, and had retention of urine. He recovered from his pneumonia two days later, but his paraplegia persisted unmodified. For a year and a half he wandered from hospital to hospital, and finally was admitted into the wards of Behier, who prescribed douches and extract of valerian. Recovery was complete in forty-five days. The man resumed his occupation and again became as quiet as ever, no longer presenting any nervous spells.

[1] Roger. Du tremblement hystérique. La semaine médicale, Nov. 5, 1893, p. 522.

Thirty-three years later, in 1893, this man had another attack of pneumonia. He easily recovered from it, but he experienced an increase in the urinary disorder from which he had suffered for some time and which was due to hypertrophy of the prostate gland. He was convalescent when he tried to catheterize himself, and, not succeeding, he became impatient, and suddenly had a nervous paroxysm similar to the one he experienced in 1860. When he became conscious he found his extremities trembling intensely. The lower limbs were rapidly cured, but the disorder persisted in the upper extremities, and it was for this reason that the patient asked to be admitted into our wards in 1893.

There can be no doubt as to the hysterical character of the phenomena, both paralyses and trembling. This diagnosis was confirmed by the fact that our patient presented a slight right hemianesthesia and a hysterogenic zone on the testicle of the same side. The absence of ocular disturbances, the diminution of the patellar reflex, and, on the other hand, the absence of the characteristic stiffness, were not consistent with the idea of spinal sclerosis and paralysis agitans, diseases the coexistence of which with hysteria is not impossible. Further developments fully proved the correctness of our diagnosis. We prescribed a daily dose of 4 grains of extract of valerian. There was improvement in a few days. One day, after catheterization, the patient had an intense febrile paroxysm. The fever did not last, but exerted, it seems, a favorable influence upon the nervous symptoms, which gradually diminished, and between June 27th, the day when the fever occurred, and July 3d it had almost completely disappeared. He could hold a large object, such as a glass, and could therefore drink all right, but he could not control his movements when handling a small article like a spoon, and hence he was not yet able to eat his soup. From this moment onward I noted his improvement day after day, by causing him to write. At first he was able to use only a pencil, and later a pen. On awakening in the morning, while his bladder was full, he wrote with great difficulty; the characters were often indented and jagged as in paralysis agitans. A few minutes after he had been catheterized he was able to write in a correct manner. These last manifestations also gradually vanished, and the man was completely cured by the end of July.

This observation seemed to me interesting in more than one respect, and particularly by reason of the conditions which governed

the development of the morbid phenomena. Here is a man who presented no hysterical manifestation whatever until the age of thirty-five years, but his nervous system had an hereditary taint. A pneumonia supervened and broke the unstable state of equilibrium. Simple anger sufficed to give rise to the gravest manifestations. Then order was again restored in the nervous system, and the man led a perfectly calm life for thirty-three years, until at the age of sixty-nine years—when man is commonly secure from hysteria—hysterical incidents once more occurred, brought about by similar causes. Much has been said in recent years regarding the rôle of infection in the development of hysteria; there can be found no observation more demonstrative than the foregoing.

In this connection I may cite the case of a young girl, aged seventeen years, who, after a facial erysipelas, was suddenly attacked by trembling in the lower extremities and the forearms. A few months after, as the result of an hysterical attack, the trembling suddenly disappeared. This abrupt termination and the appearance of hysterical attacks, which recurred once a month thereafter, confirm the diagnosis of post-infectious hysterical trembling made in the old man's case.

In the case of a girl eight years of age, five days after recovery from scarlatina, choreiform movements with anesthesia in the extremities of the left side made their appearance. A few days later a well-marked hysterical paroxysm occurred. In fifteen days all symptoms disappeared.

Another patient, also convalescent from scarlatina, developed spasmodic paraplegia in the lower extremities, with hyperesthesia, exaggeration of the patellar reflexes, and epileptoid trepidation. These manifestations disappeared within a fortnight.

Among hysterical manifestations observed after infections I may mention a case of aphasia following measles in an eight-year-old child, and two cases of astasia-abasia following scarlatina. One of the latter concerned a woman for ten years subject to hysterical attacks. The manifestations soon disappeared.

Epilepsy, Tetany, Chorea. Like hysteria, epilepsy may appear in consequence of acute infections, such as scarlatina, measles, variola, typhoid fever, and in the course of chronic infections—paludism and syphilis. The same is true of neurasthenia, which at times develops or is aggravated after infections. Paralysis agitans has also been observed on the occasion of a typhoid fever, acute

articular rheumatism, and intermittent fever. Tetany has been noted under the same circumstances, notably after the eruptive fevers, cholera, and pneumonia. Of all the neuroses chorea occurs most frequently under these conditions. Rheumatic infection—since rheumatism is now admitted to be an infection—may be held to be the most frequent cause of chorea. It seems, however, that chorea is to rheumatism what tabes dorsalis is to syphilis: it is the chief occasional cause, nothing more. There are many observations of choreic children who have never had rheumatism, but who have just suffered from some acute disease, an eruptive fever, notably measles, typhoid fever, cholera, whooping-cough, or influenza.[1]

In a total of 300 chorea cases Triboulet recognized 100 patients who developed the neurosis in consequence of some infection. On the other hand, on tabulating various statistics, I find rheumatism in the etiology of chorea in only 22 per cent. of the cases. It may, therefore, be concluded that rheumatism plays a considerable rôle, but is far less important than many authorities assert.

Infectious Meningites. The meninges, like the other parts of the organism, may be infected primarily or secondarily. The type of primary meningitis is represented by the epidemic cerebrospinal meningitis due to the meningococcus intracellularis of Weichselbaum. This pathogenic agent invades the economy through the nasal fossæ. Primary meningitis may also be dependent upon common bacteria; it is usually caused by the pneumococcus, and represents the localization of a bacteremia.

The investigation of microbes in meningitis acquires to-day considerable interest, since it is possible to puncture the spinal meninges during life and examine the spinal fluid. By this new procedure it has been found that out of a total of 100 cases of meningites 60 were due to the pneumococcus (Netter). This micro-organism may give rise to primary meningitis, or else invade the meninges in consequence of a pulmonary localization; meningitis is said to occur once in two hundred cases of pneumonia. The pneumococcus may likewise act as a secondary agent in the course of another infection, notably erysipelas.

Next comes the streptococcus. It produces the meningitis of puerperal infections and of pyemias. It is also the microbe most commonly found in meningitis consecutive to lesions in the ear.

[1] Triboulet. Du rôle possible de l'infection dans la pathologie de la chorée. Thèse de Paris, 1893.

Bacilli, notably the typhoid bacillus, Friedlaender's bacillus, and the bacillus of influenza may also induce meningeal inflammations. Rheumatic meningites seem to represent a localization of pseudo-rheumatisms—*i. e.*, of pyemias. It is also to be remembered that the association of these various microbes in the same focus is not an uncommon event.

Among the diseases treated in our wards, erysipelas furnished the strangest results. In a total of 2411 patients we observed three cases in which the necropsy disclosed a suppurative meningitis. It was natural to refer the lesion of the meninges to streptococcic infection; bacteriological examination demonstrated, however, that the process was one of secondary pneumococcic infection.

Meningitis has been altogether exceptional in connection with other infectious diseases treated by us. We find only four observations of this kind, which are very few in view of the large number, 7778, not including erysipelas, contained in our general statistics. In two instances meningites were consecutive to suppurative otitis.

Influence of Infection upon Neuropathies. The fact that an infection may give rise to nervous disturbances has repeatedly been referred to. It produces hysterical, choreic, epileptic or exophthalmic manifestations in predisposed subjects. Occasionally it arouses a past disorder. Thus in a tabetic subject of forty-five years of age, who had a syphilitic history, an attack of erysipelas caused the return of fulgurating pains, from which the patient had not suffered in several years. In other instances infection engenders morbid symptoms in apparently healthy individuals, and thus reveals the existence of a latent disease. Such was the case in a man of forty-eight years, who had had syphilis twenty-six years before. After an attack of erysipelas he complained of very intense hyperesthesia and lancinating pains in the lower limbs. Examination then revealed exaggerated cutaneous reflexes, abolition of tendon reflexes, inequality of the pupils, suppression of accommodation to light, slight ataxia in movements, and inability to walk with closed eyes. The phenomena of cutaneous hyperesthesia soon subsided, but the other manifestations, which became apparent at the time of the erysipelatous attack, continued their evolution.

On the other hand, an intercurrent infection may cause the disappearance of pre-existing nervous symptoms. It may thus act upon hysteria, epilepsy, and may, perhaps, even improve organic lesions. A woman of forty-four, who had been treated in a hospital

for two years for a paraplegia attributed to myelitis, came under my observation. During convalescence from an erysipelas the reflexes which had been abolished reappeared, paralysis diminished, and two weeks later the patient walked with ease. No sensory disorder or hysterical stigmata existed in this case. Unfortunately, in the majority of cases, amelioration is not permanent. Contrary to expectation, infections and inoculation of microbic toxins do not cure epilepsy.

Action of Infections upon the Organs of Sense.

The study of the organs of sense usually goes with that of the nervous system.

The frequency of oculo-nasal catarrh at the beginning of measles is familiar. It figures among the initial symptoms, and is of much diagnostic value. It may, however, be absent, or so slight as to readily escape observation. On the other hand, other infections, notably scarlatina and variola, are sometimes attended by the symptom under consideration. The physician must, therefore, be awake to this double source of error.

During the stationary period of and convalecsence from infectious diseases, complications, generally of a suppurative character, are very frequently observed in the various organs of sense. Purulent rhinitis occurring in scarlatina is sometimes so profuse as to suggest glanders. This complication is quite grave, as thirteen of such cases ended fatally.

The nasal fossæ may also serve as entrance to many other pathogenic germs. In several instances in which streptococci had engendered slightly purulent inflammation in the nose, erysipelas developd a few days later. The development of streptococcic dermatitis is far oftener preceded by coryza than by angina.

Ocular suppurations are rare. Catarrhal conjunctivitis is frequently observed, but it is slight and transitory, except in variola. In this infection conjunctivitis is frequent and grave. Inflammation too often extends to the cornea, and opacity may be produced within twenty-four hours. This involvement may occur even when stagnation of the septic fluids is prevented by frequent lavage. Keratitis may be superficial or ulcerative. It may terminate in perforation, with hernia of the iris, or the infection may extend to the deeper parts, producing purulent disintegration of the eye and final atrophy.

Erysipelas also may give rise to lesions of the eyelids, abscesses and even gangrene, but all these subside very readily.

Otitis media is very rare in variola. Out of a total of 755 cases ending in recovery I find it noted only in ten instances. Suppuration of the ear is sometimes observed in erysipelas, but is simply an involvement of the external ear, and is devoid of gravity.

In the majority of cases otitis occurs at the end of the disease or during convalescence. The beginning is marked by pain and persistence or recurrence of fever. Whether the tympanum is opened spontaneously or by paracentesis, the symptoms subside with satisfactory rapidity, and in most cases recovery is obtained and hearing is preserved intact. Some patients, however, left the hospital with a purulent discharge. In some rare instances otitis gives rise to alarming manifestations. One patient exhibited meningeal disturbances which rapidly yielded to the influence of bromide. Three others, suffering from post-rubeolar otitis, developed mastoiditis and were transported to a special hospital. Finally, two children died of septicemia as a result of post-rubeolar otitis.

Apart from the lesions resulting from propagation or a superadded infection, disorders which seem to be dependent upon some toxic central lesion may sometimes occur. Thus, during convalescence from the most varied infections, amaurosis, optic neuritis, deafness or vertigo due to labyrinthine lesions, may occur. According to my statistics, however, such manifestations are exceptional.

Cutaneous Manifestations in Infections.

In the course of infections the nutrition of the skin is more or less profoundly disturbed. This is clearly evidenced by the dryness and frequent desquamation of the integument, even in the absence of eruptive fevers, the frequency of suppurations and, in a great number of instances, the secondary disorders occurring in the adnexæ of the skin—the loss of hair and the trophic alterations of the nails, which become brittle or fissured. These various manifestations are appreciable, particularly in those infections which have a certain duration. They are most readily studied in typhoid fever. During convalescence, especially in children, a furfuraceous desquamation of the lateral regions of the body occurs.

In some instances the cutaneous infection is of external origin, and sometimes appears alone. At other times it occurs in connec-

tion with an infection which, by disturbing the organism, has played the rôle of a predisposing cause.

In another group are to be placed those cutaneous infections which, unlike the preceding, are of inward origin, and are effected from within outward. The same microbes are sometimes concerned in both cases, and the symptoms also may be identical. The mechanism, however, is altogether different, and the evolution follows a course peculiar to each group. The cutaneous lesion is the result of a discharge tending to throw out the infectious germs which have invaded the organism. Not only the figurate elements, but also the soluble substances are thus eliminated by the skin. This leads us to a third group of manifestations—*i. e.*, symptoms or complications of a toxic order occasioned by the poisons which are produced in the economy, and may be compared with similar manifestations observed in a great number of exogenic intoxications.

Excepting the cases in which the pathogenic agent is directly inoculated, as occurs in tuberculosis, glanders, and, at times, with the pyogenic cocci, the apparently spontaneous development of a cutaneous lesion is always referable to some previous disorder in the organism. There has been an infection, some digestive disturbance, or a nutritional disease, such as diabetes. In subjects thus predisposed there may often be found some occasional cause—friction, slight traumatism, biting, superficial excoriation, application of irritating substances, exposure to physical agents, heat, light, and, finally, cold. While it can no longer be admitted that cold is of itself sufficient to create erysipelas, it is certain that it singularly predisposes to it.

One remarkable character of cutaneous infections is the facility with which they return; relapses and recidives are almost the rule. Repeated recurrence of furunculosis and erysipelas are familiar illustrations of this fact. As far as erysipelas is concerned, it is certain that the infection is not terminated after an apparent recovery, if certain vasomotor disorders persist. These disorders are sometimes transitory and sometimes permanent. In the former instance, a slight occasional cause, a movement, an emotion, at times simply the exercise involved in speaking, is required in order to cause the face to become scarlet. In other cases the patient retains a permanent red color. At the end of several weeks this color still persists. The patient believes himself completely cured; as soon, however,

as he becomes tired, or exposes himself to cold, a new attack of erysipelas occurs.

There is another group of infectious lesions of the skin which, as already stated, are due to microbic discharge. Pyodermias are frequent in children, the germs commonly penetrating from without. In certain cases, however, analogous lesions are brought about by a galactophoritis of the mother: the pus cocci are ingested by the child with the milk, and are subsequently eliminated by the skin, causing the development of pustules.

Lesions produced by microbic elimination through the skin are at times erythematous or papular. The type is furnished by syphilides. The contagious character of papular syphilides, at least when they are moist, leads to the conclusion that they represent a localization of the morbid agent. A similar mechanism has been suggested with regard to the lenticular roseate patches of typhoid fever. By puncturing them Neuhauss claims to have found the bacillus of Eberth; the researches of Chantemesse, however, have always been negative.

The most interesting microbic eruptions are those of varicella and variola. These differ clearly from each other by their objective characters. In varicella the eruptive element is constituted by an oblong bulla with irregular borders and a clear, transparent fluid. This bulla is an elevation of the most superficial part of the skin, raising only the epidermis. In variola, the eruption assumes the form of a papule, then that of a pustule, which is rounded, hard, and seated deeply in the skin. Varicellar eruption appears in successive outbreaks, so that the most closely situated cutaneous lesions are of different ages; crusts are found alongside of transparent bullæ. In variola the lesions are of the same age, at least in the same region; for the eruption may already be crusty upon the face and hands, while it is yet pustular upon the legs. It is also to be remembered that every papule does not follow its complete evolution; hence, at the end of the disease the appearance is not exactly similar, although all the papules may have appeared simultaneously.

Exanthemata of the Eruptive Fevers. The study of the eruptive fevers raises a few problems of great interest which cannot be solved in a definitive manner until the microbic agents producing them are known. For the time being a few considerations may be presented on this subject.

The eruption, which is considered so characteristic of the group of eruptive fevers, is not indispensable. There are on record numerous cases of slight fevers, of measles and notably of scarlatina, without cutaneous manifestations. On the other hand, epidemiological investigations have shown that individuals have contracted scarlatina from patients who suffered simply from anginas; on the other hand, scarlatinal patients have transmitted simple anginas. Several of our nurses attending scarlatina patients have suffered from sore throats without any eruption or desquamation whatever.

In order to explain these facts, several hypotheses may be advanced. These apparently non-scarlatinal anginas are either slight scarlatinas, or else a common microbe, the streptococcus, exalted in the throat of a scarlatinal patient, may produce an angina in other individuals. On the other hand, the microbe of a simple angina may favor the development of the scarlatinal germ. Finally, another hypothesis consists in considering scarlatina as dependent upon a streptococcus which gives rise to typical scarlatina or to a simple angina, as the case may be.

If the last theory is admitted, scarlatina would accordingly be an angina with erythema. Several arguments may be advanced in support of this conception. Even leaving aside those arguments which could be derived from the etiology, the cases of simple anginas with erythema may still be cited. These are not cases of scarlatina, since the eruption has not the same objective characters, no desquamation takes place, and the tongue is not red and raw-looking. Moreover, the eruption is contingent, and the skin does not contain the germ of the disease: the microbe is found in the saliva. Finally, when the throat affection is absent, and this is exceptionally the case, there exists a microbic focus where the erythogenic toxins are elaborated; it is a cutaneous or mucous membrane wound, as in surgical and puerperal scarlatinas. On the other hand, bacteriological investigations detect in the throat and, if the patient dies, in the blood, in case of a complication occurring in the secondary focus, one and the same microbe. This microbe is likewise found in the urine in case of nephritis. The microbe in question is the streptococcus, which is held by some to be a common one; by others, one possessed of special characters. It is conceivable that, taking ground on these facts, certain authorities should have considered scarlatina as a streptococcic infection; a microbic focus is, in most cases, developed in the throat, and the toxins which are there pro-

duced give rise to the erythema, the importance of the eruption thus being reduced considerably. Such is the view advanced first by Klein, and subsequently well developed by Bergé.

The hypothesis is seductive. For its demonstration, however, it should be established that the organism of an individual suffering from or cured of scarlatina exerts a special influence upon the streptococcus. The agglutinating action of the serum of scarlatinal patients should, for example, be studied. The streptococci of scarlatina, however, do not occur united in masses, and it is, therefore, difficult to study their agglutination. At my suggestion, Dr. Courtain attempted to inject into rabbits the urine of scarlatinal patients, and noticed that at the end of some time the serum of these animals acquired a certain protective power against the streptococcus of scarlatina. The experiments of the author, however, are not yet sufficiently numerous to render the results conclusive.

The same reasoning is applicable to measles. This disease is especially contagious in the catarrhal stage prior to the appearance of the eruption. This fact leads to the question whether the process is not an infection of the nasal mucous membrane giving rise secondarily to a toxic erythema. The researches of Dr. Lesage seem to confirm this view.

Mechanism and Variability of Infectious Erythemata. The frequency of erythemata in the course and as a result of the most varied infections demonstrates that microbic toxins exert a very marked influence upon the vasomotor centres. They stimulate the vasodilators and enable them to react with the greatest facility. I have already referred to a new proof of this action, viz., the cutaneous redness persisting after erysipelas.

This action of infections, and notably of streptococcic infections, accounts for the curative influence exerted by some of them. Rebellious skin lesions, ulcers upon the legs, and lupuses have been seen to heal in consequence of an intercurrent erysipelas. On the other hand, vasomotor disturbances may awaken dormant lesions; in one case an erysipelas of the face seemed to renew an eczema of the hands. In a man, twenty-three years of age, erysipelas provoked a renewal of papular syphilides. This man had suffered a year before from an indurated chancre and a roseola. The fresh cutaneous manifestations yielded in a week to specific treatment.

The erythema of eruptive fevers varies in intensity, sometimes without any apparent cause, sometimes for reasons that are readily

comprehensible. Thus in children suffering from whooping-cough the rubeolar eruption is remarkable for its intensity. I had the opportunity to observe two patients who had been taking copaiva for a few days for gonorrhea. This medicine, which is capable of producing erythemata, imparted some particular characters to the eruption of an intercurrent measles. One of them, eighteen years of age, presented an eruption remarkable for the existence of very large patches of red purple color on the chest, abdomen, and the extremities. The modification was more profound in the other case, a young man twenty-one years old, who had upon his face the classical eruption, while upon the thorax the lesions were confluent and intensely red, recalling the exanthema of scarlet fever; upon the abdomen, thighs, and arms were seen extensive slightly ecchymotic patches of a livid red hue, disappearing incompletely on pressure.

In some instances the intense congestion terminates in hemorrhage. The eruption is then slightly petechial, though there may be no other serious manifestation. In certain cases of scarlatina or measles the eruption does not disappear on pressure; the skin becomes white, but a multitude of small red spots can be seen. These minute hemorrhages, even when extensive, have no grave significance. Similarly, in variola the so-called scarlatiniform rash, which has been well distinguished from true hemorrhagic rash, disappears only in an incomplete manner on pressure. In more severe cases veritable cutaneous hemorrhages occur. They are sometimes more or less extensive ecchymoses; at other times, well rounded and localized spots. These characterize a special dermatological type—purpura—which in some cases appears as an isolated manifestation, constituting infectious purpura, and in other instances as a symptom in the course of a disease, such as measles, scarlatina, and especially variola.

Relationship Between Intensity of the Eruption and Gravity of the Disease. Barring certain cases in which the eruption is incomplete, others in which the cutaneous manifestation seems to subside rather too soon, for instance, when the eruption of measles disappears on the appearance of a bronchopneumonia, it may be broadly stated that the more profound the infection the more intense is the exanthema. We do not say graver, since it is hardly possible to establish a perfect equation between the intensity and the gravity of a case. Variola alone is an exception to this rule. In this infection prognosis is to be based upon the character of the eruption

rather than upon the general phenomena. We have often seen hemorrhagic variola occur in patients whose state, at our morning visit, seemed to be excellent; there was no high fever, delirium, or marked pain; all that could be noted was a little toxic dyspnea. A few hours later, dyspnea was intensified, and before the end of the day the patient was dead, retaining consciousness to the last. By taking into serious account the eruption it is possible to make a prognosis which is always verified by the events, but which astonishes those who have never observed an epidemic of variola.

In the suppurative forms, likewise, the prognosis must be based upon the intensity and course of the eruption.

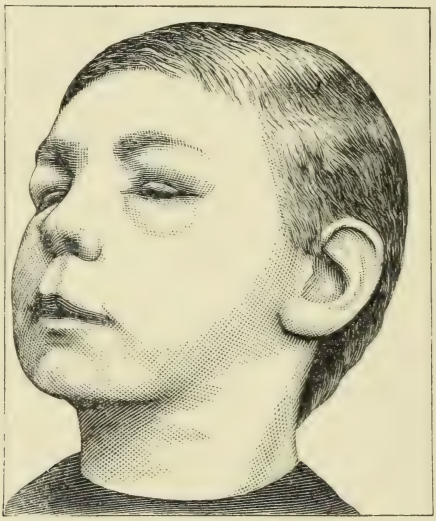
It is customary to divide variolas into two varieties: true variolas and varioloids, according as the pustule evolves or aborts. It is necessary to remark that in varioloid the eruption does undergo pustulation. While, however, in variola the pustule ruptures, and an outward suppuration is produced, attended by secondary fever, in varioloid the pustules remain closed. These dry and are covered with a brown crust; but since they do not run a course of complete evolution, the fever of suppuration is lacking.

According to the intensity of the eruption, true variola is said to be discrete, coherent, or confluent. The elements of eruption may be confluent from the first, or may later become so by fusion and growth. As, however, the intensity of the eruption varies according to the territories observed, it has been agreed that the epithet must be applied according to the state of the eruption upon the face. At all events, the eruption is generally abundant upon the face; only those cases in which a previous irritation has made another part of the skin the point of attraction must be excepted.

It is necessary to consider the condition of both the skin and of the mucous membranes. A profuse eruption in the throat, by embarrassing deglutition, hinders alimentation and greatly aggravates prognosis. Not only the number but the evolution of the lesions is also to be taken into account. If the pustules, even though very numerous, remain well separated and, as a result of the swelling of the skin, do not become confluent, recovery is probable. Not infrequently these pustules are filled with a yellowish fluid, grow and assume an acne-like aspect; this is also a favorable symptom. On the other hand, when there is no edematous swelling in the face and hands, when the pustules touch each other, and particularly when they fuse, the prognosis is bad.

At a later stage of the evolution, if the crusts developing upon the pustule are unctuous and yellow, prognosis is favorable. If, on the contrary, the crusts become dry and blackish, prognosis is almost fatal. It is to be noted in certain cases, even of true variola, that some pustules abort; they are prematurely covered by a blackish crust. The latter appearance assumed by certain isolated pustules should not be confounded with the black desiccation of the confluent elements, for premature desiccation is of good prognosis; it indicates that the organism is capable of struggling, since it is rapidly victorious at certain points. Lastly, though even secondary hemorrhages aggravate prognosis, it is well to remark that sanguinolent effusions

FIG. 33.



Post-erysipelatous pachydermia.

occurring tardily in certain pustules, notably in those of the hands and feet, are compatible with a favorable prognosis.

Consequences of Cutaneous Infections. According to the nature of the process, the cutaneous manifestations hitherto described may disappear without leaving any traces, or may be followed by cicatrices. Erythemata, exudative inflammations, even when they have disturbed the cutaneous nutrition to the extent of producing abundant desquamation, are completely cured. When, however, even simple edematous forms of dermatites are repeated, a certain degree of pachydermia may be a sequel. This occurs especially after erysipelas. In some cases the lobule of the ear, in others the face,

remains thickened. In the case of a little girl of ten years (Fig. 33), who had several attacks of erysipelas in three years, developed post-erysipelatous pachydermia of the face. As may be seen in the figure, her cheeks remained swollen, the upper lip protruding, and the eyelids were so deeply infiltrated as to partially cover the eyeballs. The visage had, however, retained all its mobility and the child all her intelligence. This morbid state could, therefore, readily be distinguished from pachydermia resulting from thyroideal incompetency.

Without dwelling upon the vesiculobulbar infections and suppurative and gangrenous lesions which are almost invariably followed by cicatrices, I shall only remark that, while the eruptions of herpes evolve without leaving any traces, the eruptions of herpes zoster terminate in cicatrices remarkable for their pigmentation and the sensory disorders surrounding them.

Clinical observation seems to demonstrate that the *sebaceous glands* are particularly involved in variola. The cicatrices are especially abundant and deep where these glands are most profusely distributed, namely, upon the forehead and nose. In some patients convalescent from grave variola we have noticed the persistence of whitish-yellow productions after the crusts had dropped off, which are nothing else than altered sebaceous products, at times simulating pustules. They may last for two or three months.

The Sudoral Secretion. Vasomotor modifications may properly be distinguished from secretory changes on the ground that while cutaneous congestion certainly favors perspiration, diaphoresis may often be observed in conditions of vasoconstriction; the expression "cold perspiration" well indicates this peculiar state.

Certain infections have the property of diminishing considerably the sweat secretion. The skin becomes dry, as is the case in scarlatina and in most of the grave infections. The return of moisture is a prognostic sign of importance. On the other hand, there are some infections diseases attended by such profuse sweating as to constitute a source of particular discomfort for the patient. The type of such infections is represented by sudor anglicus, the sufferers from which seem to be plunged in a vapor bath. The same is observed, though to a less degree, in acute articular rheumatism. There are also certain diseases in which the sweating occurs, not during the entire course, as in the preceding examples, but at a

certain moment of the evolution of the disease. Malarial as well as symptomatic intermittent fevers present a stage of sweating at the end of each paroxysm. Such is the case in paroxysms due to deep-seated suppurations and pyemic conditions.

Sweating may become manifest at certain moments in the course of typhoid fever; in general, however, patients do not complain much of perspiration. Along with the habitual form of typhoid may be placed a sudoral type, well described by Jaccoud—from the very beginning sudoral paroxysms are observed, which recur during the entire course of the disease, and at times persist during convalescence.

Perspiration is quite copious in measles and discrete variola, but is absent in grave cases of the latter infection. Finally, copious sweating is frequent in tuberculosis, in which disease it often appears from the beginning of the infection, and presents the peculiar character of being produced during the night, or, more exactly, during sleep and on awakening. It is generally localized to the chest, and annoys the patient considerably; hence clinicians are now generally agreed that it should be combated by means of antidiaphoretics.

Cold perspirations must not be overlooked. The skin is cold, pale, sometimes bluish; certain regions, notably the forehead and the hands, are covered with a viscid perspiration. This state is observed in cases of collapse, asphyxia, and in the agonal stage of all infections. It is marked in choleric patients succumbing in collapse as well as in diphtheritics suffocating by reason of a laryngeal pseudomembrane.

We have too little information as to the chemical constitution of sweat in the course of diseases to know whether it serves to eliminate toxic principles. Such, however, seems to be the fact in the light of investigations pursued by Arloing, Charrin, and Mavrojannis concerning the toxicity of this secretion. It is further known that perspiration may serve to eliminate bacteria; in the course of septicemias and pyemias sweat glands have more than once been found capable of excreting the *staphylococcus aureus*.

The Muscular System in Infections.

Typhoid fever is the only disease in which the anatomical modifications undergone by muscles in infections have been studied. The muscles of individuals dead from typhoid are dark red, and look dry and bloodless on section. Three varieties of degeneration

are detected under the microscope: granular, waxy, and vacuolar, which involve only the contractile substance, while the nuclei and protoplasm surrounding the latter proliferate. Alongside the degenerated fibres, however, there are found others manifesting cellular regression well described by Krösnig and by Durante. This is a return of the fibre to its embryonic state. This modification will probably be found in all infections, and will confirm with reference to the muscular tissue the law of rejuvenation of the organism, which has already explained many other modifications occurring in the course of the most varied infections.

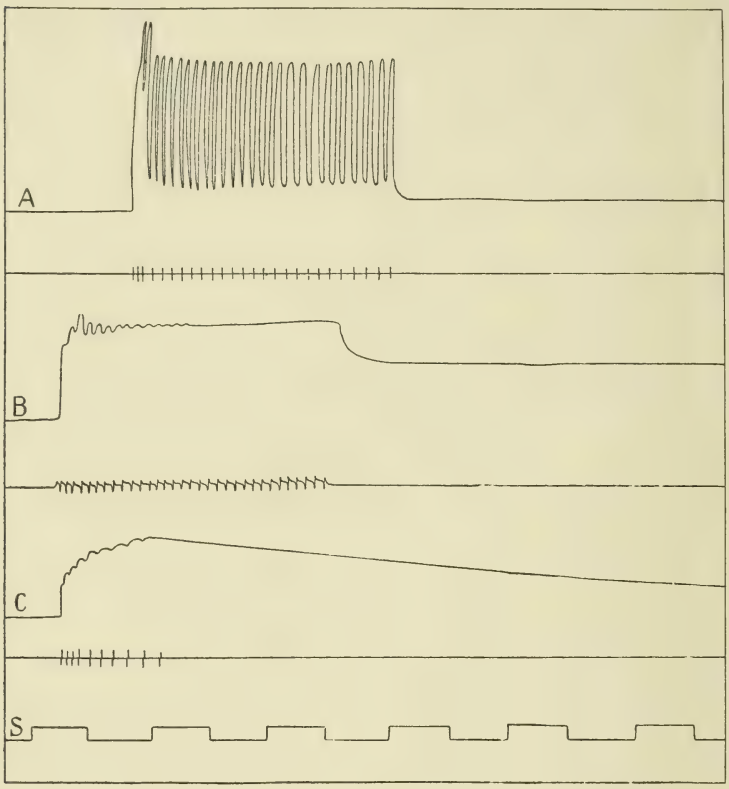
The muscular alterations account for the occurrence of partial ruptures and the production of hemorrhagic foci and even muscular abscesses. It is known, however, that suppurative myositis is an incident of very rare occurrence.

Action of the Colon Bacillus Toxins Upon Muscular Contractility. It would be interesting to inquire as to functional modifications occurring in the course of infections and first to determine the influence exerted by microbic toxins. My researches on the secretions of the colon bacillus elucidated the action of toxins upon the nerve centres as well as upon the muscular tissue.[1] It will be remembered that the colon bacillus toxin when injected into frogs produces a poisoning which may be described as follows: first, initial paresis; then, convulsions, and finally, terminal paralysis. Muscular excitability is not modified or is slightly increased during the first period. At the end of the second period important modifications are observed: when a series of excitations are caused either by acting directly upon the muscle or through reflex action—*i. e.*, by applying the electrodes at more or less distant points of the organism, relaxations follow contractions with remarkable slowness, so that these contractions very closely approach a state of tetanus. This may readily be seen by comparing the lines of Fig. 34. The first line represents the normal contractility of the muscle under the influence of a faradic current, the others represent the modifications under the influence of toxins administered. These lines are analogous to those given by fatigued muscles. These experiments show that the colon bacillus secretes in bouillon a poison capable of affecting the spinal cord and the muscles—*i. e.*, the muscular tissue itself or the terminations of the motor nerve.

[1] Roger. Etude sur la toxicité des produits solubles du Bacillus coli communis. Archives de physiologie, 1893.

The foregoing facts have been confirmed by Charrin and Miss Pompilian.[1] These authors, experimenting with the pyogenic and

FIG. 34.



Contractility of the normal (A) and of the poisoned muscle (B and C).

diphtheritic toxins, observed modifications in contraction resembling those produced by fatigue.

Infectious Osteopathies and Arthropathies.

The considerations which we have presented in reference to modifications of the bone-marrow in the course of infections explain the development of certain disturbances and pains in the limbs or in the epiphyses of the joints, and account for the rapid growth often observed in young subjects during convalescence. It may likewise be asked whether the lesions occurring in the course of

[1] Charrin and Mlle. Pompilian. Influence des toxines microbiennes sur la contraction musculaire. Soc. de biologie, November 28, 1896.

gastrointestinal disorders play a rôle in the production of certain lesions in youth, notably rachitism.

Dr. Poncet has recently called attention to a tubercular pseudo-rheumatism which presents characters similar to those of true rheumatism. A few years since I observed a case of this kind. I was called to see a young girl, sixteen years of age, who had suffered for five or six days from violent pain in the tibiotarsal joints. The case had been diagnosed as acute articular rheumatism. In fact, I found the affected joints swollen, the skin white and slightly edematous, and movement almost impossible. On a closer examination I learned that the patient had emaciated, and I was struck by her facies, pallor and dyspnea. On examining the thorax I found a serous pleurisy which had insidiously developed. Then, remembering that the sister of this patient had died from acute miliary tuberculosis two years before, I attributed all the present symptoms to tuberculosis. As a matter of fact, the articular affection was cured in a week, the pleuritic exudate was more slowly absorbed, but at the same time pulmonary lesions developed, ending fatally four months later. It is, therefore, well to remember that temporary tubercular fluxions comparable to certain pleurisies and slow types of hydrarthroses and white tumors may occur in the articulations.

Among acute infections most frequently attended by articular symptoms scarlatina occupies an important position. Few patients, at least among adults, escape this quite painful but not grave complication. A day or two after the eruption, patients complain of difficulty of moving the fingers, and it may be seen that the joints of the phalanges are swollen and painful. The wrist-joint is also frequently involved, but the larger joints are rarely, if ever, affected. It is well to add that these arthropathies are far more frequently observed in women than in men, and are at times accompanied by muscular pain and hyperesthesia. In some instances these complications appear during convalescence, and then present a very different localization: they affect especially the knee-joint and then the shoulders. Whether early or tardy, these arthropathies behave like those of true rheumatism: they do not suppurate.

In measles arthropathies are rare; and the same is true as regards variola. In the latter disease the affected joint may suppurate, and its history is the same as that of multiple suppurations produced by this disease.

CHAPTER XV.

INFLUENCE OF INFECTIONS UPON THE VARIOUS PARTS OF THE ORGANISM (*Continued*).

Influence of Infections upon the Circulatory Apparatus. Functional Disorders of the Heart. Modifications in the Pulse During Convalescence. The Non-organic Murmurs. The Action of Microbic Toxins upon the Heart and Blood Pressure. Infectious Myocardites, Endocardites, and Pericardites. Cardiac Hypertrophies in Rapidly Growing Young Subjects. Action of Infections upon the Arteries. Rôle of Infections in the Development of Arteriosclerosis. Action of Infections upon the Respiratory Apparatus. The Lungs in Infectious Diseases. Classification of Pulmonary Lesions of Infectious Diseases. Pleural Lesions in Infections. Serous Pleurisies. Purulent Pleurisies. Hemorrhagic Pleurisies. Tracheobronchial Adenopathies. Remote Consequences of Infections of the Respiratory Apparatus.

Influence of Infections upon the Circulatory Apparatus.

Functional Disorders of the Heart. The action of infections upon the heart may be expressed by two kinds of phenomena—functional disturbances, and lesions. The high temperature may be held responsible for the functional disorders. In fact, when the bodily temperature rises, no matter by what procedure, the pulse is accelerated. The increased activity of combustion evidently results in acceleration of the respiratory movements and cardiac pulsations; in this manner elimination of the waste products resulting from the exaggerated organic combustion is assured.

Hyperthermia, however, does not represent the only factor accountable for the accelerated heart beats, since, if such were the case, the pulsations should always present the same frequency at the same temperature. It is true that, in adults, each degree centigrade of thermal rise admittedly corresponds to an increase of ten pulsations. For instance, if the temperature rises to 105.8° F. (41° C.), the pulse rises from 80 to 120. Such is not always the case, however. Certain fevers induce greater acceleration of heart beats than others. For instance, in scarlatina the pulse is far more rapid for the same degree of temperature than in other infections. It is, therefore, probable that toxins directly or indirectly influence the movements of the heart. It is, moreover, known that an unusual acceleration in the heart beats in the course of an infection suggests

some complication—paralysis of the nerve centres, myocarditis, a visceral lesion, a profuse hemorrhage, and, in typhoid fever, an intestinal perforation.

During convalescence a subnormal temperature often coincides with a pulse less rapid than normal. Some patients, especially children, may present at this time an irregular pulse. To the uninformed physician this functional disorder may suggest a myocardiac involvement. During the stationary period cardiac irregularities are of more serious significance, and should draw the physician's attention to the condition of the myocardium. It is to be noted, however, that in cases of erysipelas with normal temperature or a temperature slightly above normal, whether the pulse is slow or rapid, marked irregularities in the cardiac movements may occur at all ages and even in very benign cases. Irregularity and intermittence of the heart beats may also be observed in cases of scarlatina; and, though they are particularly frequent during convalescence, they may likewise be met with during the stationary period.

The absence of symptoms ascribable to a myocardiac lesion leads to the admission that these various manifestations depend simply upon nervous influence.

Non-organic Murmurs. Murmurs presenting all the characters of extracardiac murmurs described by Potain are very frequently heard in the most varied infections. These murmurs are not rough; they are mesosystolic, exceptionally mesodiastolic. Their intensity varies from one moment to another; they diminish or disappear in the sitting posture, and remain localized at the points at which they originate. They are usually observed in scarlatina, and are more frequent in women than in men. These murmurs are of rarer occurrence in children; they nevertheless occur, and may be heard even in young subjects five or six years of age. Their frequency in scarlatina is about 22 per cent.

The murmurs of typhoid fever possess the particular character of being pre-infundibular; they appear as early as the end of the first week, which indicates that they depend, not upon post-infectious anemia, but upon the fever itself. Potain attributed them to febrile excitation of the heart. They are, perhaps, connected with a slight degree of myocarditis and, at times, aortitis. In support of this view I must remark that, in certain instances, the extracardiac murmur suddenly gives place to a diastolic "bruit de galop" con-

nected with myocarditis. The excited state of the myocardium explains the first phenomenon; the loss of tonicity, supervening later, accounts for the "bruit de galop."

Action of Toxins Upon the Heart and Blood Pressure. Manfredi and Traversa, experimenting upon frogs, demonstrated that the soluble products of the streptococcus notably slow the movements of the heart. Gley and Charrin observed the same effects with sterilized cultures of the bacillus pyocyaneus; they moreover obtained cardiac dilatation in mammals. The latter manifestation is of considerable importance, since it tends to indicate that the extracardiac murmurs above described may be due to a slight degree of dilatation of the heart. I also undertook to study the action of the various toxins upon the frog's heart.[1] The most interesting results were obtained by means of sterilized cultures of the *bacillus septicus puditus.* These cultures, when injected beneath the skin of a frog, produce marked paresis within fifteen or twenty minutes, excitations nevertheless give rise to reflex movements, and the animal at times jumps. If, however, under these conditions, the thorax is opened and the heart exposed, this organ is found to be beating very slowly or at a standstill. This arrest of the heart occurs, therefore, at an early period of intoxication, while the other morbid manifestations have not yet become grave.

This study was recently taken up by Drs. Chantemesse and Lamy[2] who experimented upon the hearts of tortoises by means of extremely ingenious contrivances. They demonstrated that the typhoid and the diphtheritic toxins are poisons for the myocardium and produce cardiac paralysis after a period of latency. Of still greater interest is the fact that the blood of an animal which has received one or the other of these toxins, exerts an exciting action upon the heart, which action seems to be due to a new substance elaborated by the organism under the influence of the microbic poison.

These cardiac disorders, however, do not seem to be entirely due to the action of microbic poisons upon the heart; certain manifestations are probably caused by an influence exerted upon the peripheral

[1] Roger. Poison cardiaque d'origine microbienne. Société de biologie, Jan. 28, 1893; Archives de physiologie, April, 1893. Action de quelques toxines microbiennes sur le cœur. Société de biologie, Feb. 18, 1893. Etude sur la toxicité des produits solubles du Bacillus coli communis. Archives de physiologie, July, 1893.

[2] Chantemesse and Lamy. Effets des toxines microbiennes sur le cœur isolé. XIII Medical Congress, section of general pathology, 1901, p. 137.

circulation. Bouchard, Charrin, Gamaleïa, Gley, and Arloing have dwelt upon the vasomotor modifications produced by toxins. The author studied the influence of poisons secreted by the colon bacillus of dysentery.[1] This microbe has the advantage of furnishing exceedingly toxic cultures. These cultures, when sterilized by means of chloroform and injected into rabbits in the proportion of 0.25 per kilogram of animal, cause death within twenty-four or forty-eight hours. The author studied, by the graphic method, the effects produced upon the circulation and respiration. The poison evidently tended to lower the blood pressure. At a certain moment, when the pressure is considerably reduced, convulsions occur which raise the pressure, and slight improvement takes place. The morbid symptoms are soon intensified, the blood pressure continues to fall, the descending course being marked by renewed convulsions. Lastly, a rapid and final reduction in pressure occurs, and the animal dies.

These experiments show that the heart struggles against the influence of the toxin. Its contractions become more energetic and slower. The poison does not, therefore, act upon the heart, and the reduced pressure is probably due to modifications in the abdominal circulation. Intense congestion in the intestine, liver, and kidneys revealed by the necropsy seems to support this view.

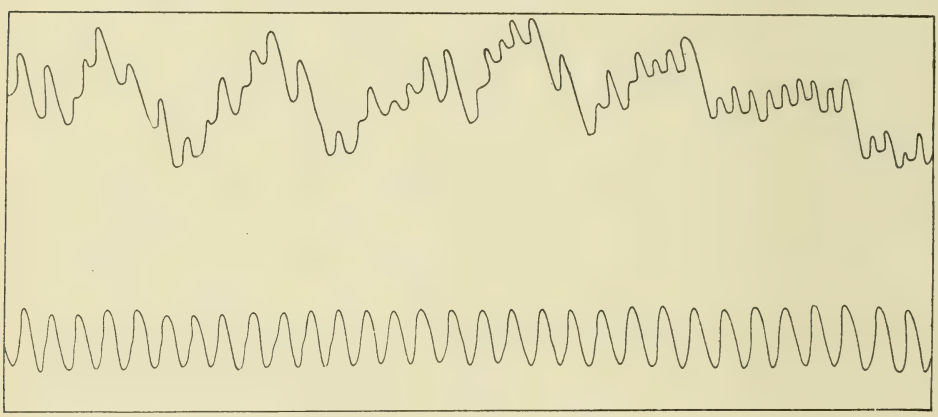
Unlike the circulation, respiration is but slightly disturbed. When 2.5 c.mm. of the cultures are injected into the veins the respiratory movements generally do not present any modification. At most they may be slightly accelerated for a few seconds. With the employment of doses twice or three times larger the movements become 136 per minute, instead of 80; the amplitude is coincidently diminished by one-third. These manifestations are transitory, however, and do not last more than fifteen or twenty seconds. At a more advanced stage of intoxication breathing is again accelerated (Fig. 35); it is then slowed. Long pauses are observed; only twenty or even ten inspirations per minute occur. The animal thus succumbs by arrest of respiration while the heart is still beating.

Comparison of these experimental phenomena with certain clinical manifestations reveals an analogy—that is, lowering in the blood pressure. The latter disturbance has often been attributed to diarrhea, which produces dehydration of the organism. Contrary to this

[1] Roger. Les toxines du colibacille de la dysenterie. Annales de la Soc. de méd. de Gand, April, 1900, p. 139. Action des toxines de colibacille de la dysenterie sur la circulation et la respiration. Presse méd., Nov. 3, 1900.

view, I conclude from experimental results that it is due to intoxication, since the toxins do not decidedly affect the myocardium. We now likewise understand why the pressure quickly rises as soon as gastrointestinal intoxication is checked or an intravenous injection of artificial serum is given to remedy the effects of peripheral vasodilatation. Finally, our experimental results offer a new illustration of the compensating antagonism existing between the peripheral and central circulation. By the increased energy of its contractions the heart endeavors to raise the blood pressure, which tends to fall as a result of abdominal vasodilatation.

Fig. 35.



Rapid and short respiration. Slow and energetic cardiac movements. The lower line indicates the struggle of the heart against the lowering of blood pressure. The upper line represents the respiration.

Acute Myocardites. Acute myocardites may be primary, but they generally develop in the course of an infectious disease. As is the case in other visceropathies, localization in the myocardium is favored by various auxiliary causes. Among these, the influence of age is one of the most important. The affection is commonly observed between the ages of ten and thirty years, because at this period of life the infectious diseases capable of engendering it are frequent. Heredity also plays a rôle; Benecke found in a total of twenty-eight cases twenty-two presenting evidences of congenital debility of the circulatory system. Overexertion has long been considered among the causes of acute, diffuse or circumscribed myocardites. Army physicians have often noted the frequent appearance of myocarditis in consequence of forced marches. It is at

present established that overexertion does not create alteration of the myocardium; it simply acts by lessening the resistance of the organism, and thus favors its contamination by infectious germs. The latter become localized in the heart, which, as a result of its excessive activity, is found in a state of morbid receptivity.

All infections, including acute articular rheumatism, are capable of giving rise to acute myocarditis. Typhoid stands at the head of the list; all of its forms, however, do not equally predispose the sufferer to this cardiac involvement. The ataxo-adynamic form with hyperthermia is particularly apt to induce alteration of the myocardium. Out of 152 necropsies, Hoffmann found but 54 hearts *almost* sound. In the course of the third week myocarditis almost constantly makes its appearance. Myocarditis also appears early, at times on the fifth day in grave confluent cases of variola. According to Desnos and Huchard most deaths occurring before the eleventh day of this disease must be attributed to myocarditis.

Pneumonia is often complicated by myocarditis. Only a few years ago French physicians received with astonishment Jurgensen's work, which laid much stress upon pneumonia myocarditis. At present pneumonia is found modified; its course is tedious, defervescence is tardy, and fatal termination is more frequent. We are now observing in France what Jurgensen observed in Germany a few years ago: myocarditis has become one of the frequent causes of death in pneumonia.

Streptococcic infections may also be complicated by myocarditis This involvement is rare in erysipelas, but frequent in puerperal and surgical septicemias, and may occur even in streptococcic sore-throats. Myocarditis is also encountered in scarlatina, typhus fever, intermittent fever, and acute tuberculosis. In chronic tuberculosis it seems to depend upon secondary infections. In measles it is altogether exceptional. Myocarditis is of very frequent occurrence in diphtheria, and it is often expressed by symptoms difficult of interpretation.

The *symptomatology* of acute myocarditis is divided by authors into two phases: one of erethism, and another of depression. In the former stage the heart beats more frequently and strongly. The patient complains of palpitation and precordial or sternal pain Pain may also be caused by pressing the finger upon the third or fourth intercostal space on the left side, the point which Peter called "the precordial button" (*le bouton précordial*). These dis-

turbances soon bring in their train pulmonary manifestations, notably intense dyspnea. After three or four days the second phase of myocarditis appears. The heart-beats become weak and rapid, growing gradually inappreciable by palpation. On percussion precordial flatness is found to be increased, owing to dilatation of the heart. Auscultation reveals a "bruit de galop," due to ventricular ectasis or a very soft mesosystolic or even systolic murmur at the apex. This may be due to functional incompetence of the auriculo-ventricular valves as well as to dilatation of the heart; hence the disappearance of the murmur when a movement of the patient increases the power of the contractions by arousing the energy of the myocardium. These phenomena are soon replaced by the fetal rhythm of Stokes or embryocardia of Huchard. The two murmurs of the heart are rapid and weak and can no longer be distinguished. They succeed each other after the manner of the tick-tack of a clock. Later, when the first murmur becomes so weak as to indicate an incomplete systole, and the second murmur also, in its turn, further diminishes, a fatal termination, according to Bucquoy, may be expected within a day or two. The pulse presents modifications corresponding to those of the heart. It is unequal rather than irregular. It manifests veritable intermittence only toward the end of the disease.

The period of excitation is lacking in typhoid fever. Myocarditis may even remain in a state of latency and be expressed simply by acceleration and weakness of the heart-beats; hence the occurrence of sudden death on the occasion of movement.

Differential diagnosis between myocarditis and endocarditis or pericarditis may sometimes be difficult; an error is more liable to occur as these various lesions may coexist. Modifications in the pulse must first be taken into consideration; and then it must be remembered that the murmur of endocarditis increases on movement and under the influence of any cause rendering the heart-beats more energetic. The reverse is the case in myocarditis. Moreover, the murmur of myocarditis is transitory. No doubt remains, however, as to the myocarditic nature of the events when the "bruit de galop" and especially the fetal rhythm are found.

Post-infectious Cardiac Hypertrophy. I believe that a previous infection is very often responsible for the cardiac hypertrophy of young subjects which is too readily attributed to rapid growth. There are two possible events. In some cases the development of a

lesion, such as endocarditis, is observed in the course of a disease. At this age this lesion is curable, and at the end of a few months, or a year or two at the latest, it is repaired. The subject retains a hypertrophy of the heart, however, which causes shortness of breath and troublesome palpitations of the heart to the extent of rendering walking, bodily, and even intellectual exertion, difficult. If the physician has followed the entire evolution, he attributes this hypertrophy to the valvular lesion, and considers the case one of compensating hypertrophy, somewhat exceeding the requirements of the organism and surviving the causative lesion. In other instances the heart does not seem to have been affected during the disease; no lesion of the myocardium has been expressed by the slightest murmur. Hypertrophy, nevertheless, develops, and when the patient complains of it and it is discovered, the physician hesitates to connect the apparently recent disorder with the disease of years ago. I believe, however, the mechanism to be the same in both instances. Infection, whether having affected the valvular endocardium or not, has produced lesions in the myocardium. Compensatory hypertrophy is designed to re-establish the disturbed circulatory mechanism; the effort, however, exceeds the end and terminates in a veritable lesion. Such is, in my opinion, the cause of a great number of hypertrophies attributed to rapid growth and occurring after the most varied diseases, among which typhoid fever, acute articular rheumatism, scarlatina, and diphtheria may particularly be mentioned.

Although these hypertrophies are at times quite troublesome, they are not always grave. The heart which is hypertrophied may soon cease to develop; the individual continues to grow, the chest develops, and there comes a time when the heart appears to have resumed a normal volume and regular activity. Only a long period of time after, at the end of twenty or thirty years, new disorders become manifest—*i. e.*, signs of chronic myocarditis, at times accompanied by valvular endocarditis, which is developed in an insidious manner.

Endocarditis. It is at present well established that every acute endocarditis is of infectious origin and that all infections are capable of involving the endocardium. Endocarditis may be benign or malignant and ulcerative. These differences depend in part upon the nature and virulent potency of the microbe. The state of the attacked organism, however, is of greater importance. Endo-

carditis assumes the ulcerative character when the individual is already debilitated by previous or present disease, overexertion, and evil hygienic conditions, abortion, the puerperal state, or previous lesions, which Netter has found in 50 per cent. and Goodhart in 75 per cent. of the cases.

The frequency of endocarditis in rheumatism was well demonstrated by Bouilland. It may be stated that endocarditis is the rule in grave acute, generalized rheumatism; it is exceptional in apyretic, slight, and partial rheumatism. The employment of salicylates, however, seems to diminish the cardiac complication by arresting the evolution of the disease. Endocarditis, nevertheless makes its appearance in one-fourth of the cases in adults. In children, according to Cadet de Gassicourt, it is observed in the proportion of 80 per cent. The first symptoms of the cardiac involvement are generally manifested at the end of the first or in the course of the second week. The lesion occupies the mitral, less frequently the aortic, valves, and exceptionally the right heart.

Other infections may engender a vegetative or an ulcerative endocarditis. It is admitted that the lesion of the heart is at times due to the action of the principal agent, but in a greater number of instances it must be attributed to secondary infection. Endocarditis occurring in influenza, gonorrhea, and tuberculosis results from secondary infection by the streptococcus, pneumococcus, and less often the staphylococcus. It is well to remember, however, that Koch's bacillus may be localized in the endocardium, especially in cases of acute tuberculosis. Contrary to what might be expected, endocarditis is very rare in erysipelas; the microbe exhausts its power in the skin and manifests no tendency to invade the viscera. The frequency of endocarditis in pneumonia has of late been demonstrated by numerous observations. Sometimes the streptococcus, but most frequently the pneumococcus, is the responsible agent. The cardiac complication may occur in the decline of the pulmonary infection or after defervescence. The aortic orifice is generally the point of attack, and the process is, as a rule, ulcerative. Ulcerative endocarditis is also encountered in 37 per cent. of the cases of pyemias and in 11 per cent. of puerperal septicemias. Articular manifestations often accompany the process and give it the appearance of infectious pseudorheumatism.

The vegetative or warty type develops in an insidious manner. Some phenomena, such as precordial pain, palpitation on the slightest

exertion, embarrassed respiration, cephalalgia, suggest the possibility of cardiac localization. All these manifestations, however, are inconstant. Endocarditis, may therefore, readily escape notice if the heart is not systematically examined. At the beginning of valvulitis the phenomena are those or cardiac excitation; there is as yet no murmur, since at this time the valves are soft, thickened, and incapable of vibration by the blood waves. The normal murmurs are found to be rather dull; the first especially becomes indistinct at the apex—the swollen valves still insure occlusion, but no longer snap. When the aorta is the affected part the second murmur is found dull at the base. Only at a later period do the murmurs of incompetency become manifest.

The ulcerative form may also escape attention, but for different reasons—the physician's attention is absorbed by the severity of the general phenomena. In view of these, two principal clinical forms have been described: a typhoid form and a pyemic form In the former case the pneumococcus is the habitual agent. Either at the beginning or four to six days after defervescence of a pneumonia the patient experiences a single chill and rapidly develops fever at 104° or 105.8° F. (40° or 41° C.). The cardiac pulsations are painful and frequent; the pulse is small and often irregular. Adynamia makes rapid progress. In some cases embolism occurs, giving rise to sudden hemiplegia, exceptionally to paraplegia, at which time all doubt as to the diagnosis is dispelled. In the pyemic form the dominant feature is the enormous oscillations of the fever, which occurs in the form of paroxysms, characterized by the three classical stages—chill, fever, and sweating. This is Lancereaux's intermittent form. In this type embolism is far more frequent than in the preceding. In the typhoid type the aortic orifice is generally affected; in the pyemic, the mitral.

Ulcerative endocarditis is but exceptionally curable. On the other hand, the warty form is often cured, and cured in a complete manner. The happy termination sometimes occurs so rapidly as to render the diagnosis doubtful. In a case of grave erysipelas I heard a systolic murmur at the apex. Ulcerative endocarditis was thought of, but the murmur diminished in four days and completely disappeared within a week. This evolution is not rare when the patients can be watched. I treated a little girl who suffered three times from acute articular rheumatism. During the first attack, which occurred at the age of four years, mitral incompetency was

produced, which healed in eight months. She had a second attack of rheumatism when seven years old, and developed the same symptoms, which disappeared as rapidly as in the first instance. At the age of fifteen years she had a third attack, and a systolic murmur again made its appearance, and took eighteen months to disappear. From that time on the heart remained hypertrophied; but this condition was later compensated by the mechanism already indicated. At present this individual is nineteen years old, and the heart seems to be absolutely normal.

Pericarditis. Pericarditis may represent the principal localization of an at first generalized infectious process, or it may supevene as a secondary phenomenon. It often coexists with endocarditis and myocarditis; such a pancarditis is the rule in children. As in the case of endocarditis, bad hygienic conditions, fatigue, alcoholism, and cold favor the localization in the heart. Thus is explained the occurrence of epidemics of pericarditis formerly observed in besieged cities.

The pericardiac lesion often occurs under the influence of rheumatism. The eruptive fevers may also reach the pericardium. At the eruptive period of variola dry pericarditis is said to develop; later, purulent pericarditis is found. It is rare in measles, but quite frequent in scarlatina. In the latter instance it is said to easily become purulent or hemorrhagic in character, but my observations do not confirm this statement. I have mainly found dry pericardites. During the stationary period or in convalescence friction murmur is heard, lasting for five or six days; it seldom persists for two weeks. There may be no disturbance to draw the physician's attention to the heart, or the patient may in some cases complain of palpitation and precordial pains. The beginning of the process may be marked by syncope. In the course of erysipelas I have sometimes heard pericardial frictions which disappeared after causing some pain, palpitation, and tachycardia. In two instances, however, pericarditis caused a fatal termination. A woman, seventy-two years old, suffering from a wandering erysipelas, died on the eleventh day, and the necropsy revealed a purulent pericarditis and a slight mitral valvulitis. Another woman, eighty-two years of age, also suffering from an attack of wandering erysipelas, succumbed when the cutaneous lesions were almost cured; at the necropsy a purulent pericarditis was found.

Pericarditis is frequently observed in tuberculosis; 14 per cent. of pericardites are connected with tuberculosis (Bamberger).

In some cases pericarditis is ushered in by chills, fever, dyspnea, precordial pain, at times by dysphagia. The temperature usually rises, but in certain cases it may be lowered at the moment of this complication, as occurs, for example, in typhoid fever (Charcot, Brouardel). In the majority of cases pericarditis remains in a state of latency; daily examination is required in order to discover it. It must, therefore, be systematically looked for in the course of diseases capable of causing this complication.

The nature of the effusion is of great prognostic value, for it indicates the degree of gravity of the causative process. Prognosis is favorable in cases of dry pericarditis; doubtful in cases with effusion; very grave in purulent, and fatal in hemorrhagic pericarditis. When the previous condition and age of the patient as well as the etiological conditions and general symptoms are further taken into consideration, all the elements required for a correct appreciation of the case will be at hand.

Action of Infections upon the Arteries.

Acute arteritis is not, as was once believed, a generalized process causing fever, but a localized affection resulting from fever. Its etiology may be described by a single word—infection. The most typical example is represented by arteritis of the limbs with consecutive gangrene occurring mainly in grave infections and nearly always at their decline or during convalescence.

Typhoid is undoubtedly the infection most frequently concerned in arteritis. This complication is usually observed in the lower extremities on one side, oftener on the right than on the left, and preferably in the posterior tibial, next the femoral, anterior tibial, or dorsalis pedis artery; the arteries of the upper extremities are less frequently involved: the iliac, external carotid, Sylvian (Vulpian), even the pulmonary (Hoffmann) artery. The arterioles of the viscera are often affected during the stationary period, while arteritis in the limbs seldom, if ever, appears before the third week, and sometimes not until the forty-first (Rendu), or even fifty-eighth day (Barié).

According to Leyden, influenza causes acute arteritis as often as if not more frequently than typhoid fever does. In half of the cases the popliteal is the seat of inflammation; next the femoral, humeral, axillary, cerebral, and central artery of the retina. Here also the complication occurs during convalescence.

Arteritis has been noticed in variola, especially in the hemorrhagic form of it, sometimes as early as in the period of eruption, at other times later, and, apart from the aorta, the coronary arteries are usually attacked. Scarlatinal arteritis also localizes in the coronaries, and is a complication of rare occurrence. In a total of 2213 cases observed in our wards of Porte d'Aubervilliers we found only one instance of acute arteritis in scarlatina, and that was seated in the femoral artery. In measles it has scarcely ever been observed. It is not rare in diphtheria, and involves usually the coronary, pulmonary, renal and Sylvian arteries. Erysipelas has been seen to be complicated by inflammation of the circle of Willis (Ponfick), obliteration of the nutrient arterioles of the eyeball (Parinaud), and a thrombosis of the popliteal (Schmitt). Among other infections we may cite puerperal fever, septicemias, pyemias, typhus, pneumonia, cholera, etc. I have observed cerebral arteritis with thrombosis and acute softening of the brain in the course of a gastro-enteritis. Arteritis of the limbs was observed by Legroux in acute articular rheumatism. Hanot believes that acute rheumatismal arteritis often accompanies endocarditis, but remains unnoticed by reason of the obscurity of its symptomatology. Leyden noted an arteritis of the popliteal occurring in a suppurative appendicitis. We may also mention the case of Haushalter concerning thrombosis of the Sylvian and anterior cerebral arteries in a child suffering from empyema, and the observation of Vaquez regarding a tubercular subject.

To sum up, while inflammation of the visceral arterioles is of frequent occurrence in infectious diseases, acute arteritis of the extremities is exceptional outside typhoid fever and influenza.

Acute arterites may be due to a localization of the microbic agent responsible for the principal disease; in other cases they represent a secondary infection; and in still a third class of instances toxins, independently of figurate elements, seem to be capable of producing inflammation in the vessels.

The microbes of typhoid fever, pneumonia, and erysipelas sometimes induce arteritis. On examining the myocardium in eight typhoid cases Rattone found Eberth's bacillus in the walls of the arterioles distributed to this muscle in seven instances. In almost all cases in which the arteries of the extremities are affected, inflammation is due to a superadded infection by the pneumococcus, more frequently by the streptococcus. Finally, arteritis sometimes

develops under the influence of toxins, as is undoubtedly the case in certain instances of diphtheritic arteritis. Experimental demonstrations have fully corroborated clinical observation on these points.

The first symptom of arteritis in the limbs is generally pain, increasing during the night. Rise in the bodily temperature and acceleration of the pulse also occur. Coincidently, or somewhat later, torpor, heaviness, and formication are felt in the affected limb. Pulsation in the diseased artery and its branches is at first weakened, and subsequently disappears; a supplementary circulation, however, is established which insures nutrition of the parts. In most cases the events proceed thus: the color of the skin in the diseased segment becomes whitish, its temperature is lowered, and sensibility diminished; hence a characteristic contrast between the superficial hypoesthesia and painfulness in the deeper parts results. At a later stage patches of cyanosis and even purpura make their appearance, first at the end of the limb—*i. e.*, fingers or toes, announcing the imminence of sloughing. The latter condition, however, does not necessarily occur; a sufficient collateral circulation may tardily be effected, and the limb then gradually resumes its normal characters. In other instances, after a deceiving remission, the symptoms again become aggravated, and the affection runs its course toward sphacelation. When gangrene is thus produced the danger is not confined to the limb; the toxins originating in the dying tissues induce a very grave general state. Fever, fetid diarrhea, dyspnea, delirium, and a profound adynamia are some of the features of the general condition, in which fatal termination sometimes occurs before the separation of the eschar.

Role of Infections in the Development of Arteriosclerosis. The study of acute arteritis raises a pathogenic problem of the highest interest: What is the rôle of infection in the development of arteriosclerosis?

In the first place, I think it is a well-demonstrated fact that gastrointestinal disturbances when characterized by excessive fermentations and putrefactions induce arterial changes. The question is one of veritable intoxication of the organism, and, though the liver is generally the organ most profoundly affected, the poisons sooner or later pass the barrier opposed by this gland and exert their action upon other parts of the organism, notably upon the arteries and the main emunctory, the kidney.

The influence of temporary infections is not as simple as that of intestinal putrefactions. Numerous clinical observations, however, demonstrate the reality of this etiological factor. Guéneau de Mussy claimed to have seen the arteries suffer a rapid fibrous transformation in the course of an attack of rheumatism. Parrot noted the development of infectious arteritis of the aorta in childhood, discovering atheromatous points at the root of the coronary arteries. Landouzy and Siredey have shown that arterial lesions are far more extensive than was once believed, and terminate in arteriosclerosis. It is true, however, that in the acute period arterial lesions predominate at certain points; the same is true as regards the chronic forms. The arterial system is not affected throughout in the same degree.

In this connection the influence of chronic diseases such as malaria, syphilis, and tuberculosis is by no means less important. Here also it is true that the lesions produced by syphilis are circumscribed; hence Lancereaux and Heubner deny to this disease all influence in the production of arteriosclerosis. I believe Cornil is right in attributing to syphilis certain cases of atheroma occurring in young subjects in the absence of any other appreciable cause. The influence of tuberculosis seems more certain. The experiments of Vissman and of Thérèse demonstrated that intravenous injection of dead bacilli or of tuberculin is followed by diffuse arterial alterations. On the other hand, H. Martin and P. Teissier have pointed out the hardness of the arteries in certain young tuberculous subjects in spite of lowered blood pressure, which is the rule in tuberculosis.

Action of Infections upon the Respiratory Apparatus.

Larynx. The mucous membrane of the larynx may be the seat of catarrhal manifestations expressing the principal or subordinate localization of an infectious process. At present there is no doubt as to the microbic origin of laryngites, which were usually attributed to cold. The latter plays the rôle of an occasional cause.

Laryngitis is sometimes one of the manifestations of a general infection. In measles the larynx, trachea, and bronchi participate in the catarrhal process, which at the same time involves the mucous membrane of the nose and eyelids. During the stationary period of infections the larynx may be invaded by the morbid process. This localization is generally of little importance, but in some cases it may prove very serious. Thus in variola pustules may develop

in the larynx and induce edema of the glottis. The result is a growing dyspnea necessitating surgical intervention. This happened in five of our patients, four of them suffering from confluent, one from coherent variola. In spite of tracheotomy, these five individuals, who were profoundly infected, died. Even varicella, which is generally a benign disease, may be complicated by a laryngeal eruption of a more or less sêrious character.

Among other infections, not to mention diphtheria which, of of course, heads the list, we find erysipelas, which may present the laryngeal complication in exceptional instances: influenza, glanders, tuberculosis, syphilis, and leprosy.

Trachea and Bronchi. Tracheobronchitis is of very frequent occurrence in the course of infections. It may be produced by various microbes, the most specific as well as the most common of bacterial agents. Marfan has endeavored to classify the various types of bronchitis.[1] The following table, which we borrow from this author, gives a good idea of the main varieties encountered and of the mechanism governing their development:

- Bronchites
  - Specific
    - Bronchitis of influenza.
    - Bronchitis of whooping-cough.
    - Bronchitis of measles.
    - Bronchitis of diphtheria.
    - Bronchitis of anthrax.
    - Bronchitis of bubonic plague.
    - Bronchitis of tuberculosis.
    - Bronchitis of variola.
    - Bronchitis of malaria.
    - Bronchitis of glanders.
    - Bronchitis of syphilis.
  - Non-specific (generally due to pneumococci and streptococci).
    - By autoinfection.
      - Originating on the spot, mucous membrane altered by
        - Cold.
        - Previous specific bronchitis.
        - Chronic affection of the lungs, pleura, and mediastinum.
        - Inhalation of irritating substances.
        - Intoxications.
        - Chronic organic or diathetic affections.
        - Adynamic conditions (typhoid fever, acute diseases of long duration, cachexias).
      - Originating from distant parts
        - Spreading from the upper respiratory tracts.
        - Through the blood current.
          - Bronchites of gastrointestinal origin.
          - Bronchites by septicemias.
    - By heteroinfection
      - Contagion by inhalation.

[1] Marfan. Maladies des bronches. Traité de médecine. 2d edition, Paris, 1901, vol. vi., p. 284

The respiratory tract, at least in its upper parts, being inhabited by innumerable microbes, the most ordinary causes which directly or indirectly disturb the mucous lining may offer to common bacteria an opportunity to exert their pathogenic action. It is readily conceivable that even when bronchitis seems to be of a specific nature, as is the case in measles, a secondary infection may intervene to modify its course. The fact that (rubeolic) bronchitis is an early and constant accompaniment of measles proves that it is due to the specific parasite of the infection; it rapidly resolves, but, during its short duration may permit common-place micro-organisms to assume an aggressive attitude, and thus prolong the bronchial inflammation, and, if sufficiently exalted, give rise to bronchopneumonia.

The same is true as regards variola. Variolar pustules may be produced in the bronchi and often become the starting point of a pseudomembranous process. Apart from this specific bronchitis, ordinary bronchitis is often observed in variola, and seems to be due to the pneumococcus; such bronchites were very frequent during the Paris epidemic of 1900. We must also mention the bronchitis of typhoid fever. It is an almost constant complication, appearing on the fourth or fifth day and lasting until the period of convalescence It is generally attributed to common bacteria of the respiratory tract.

In most cases bronchitis is not of grave character; when intense, however, it may embarass hematosis and cause troublesome coughing. In weakened individuals it tends to become purulent, and gives rise to a secretion which obstructs the respiratory passages, is with difficulty eliminated, and induces secondary lesions in the pulmonary parenchyma, even bronchopneumonia. As a result of this stagnation of the purulent secretion, gangrene in the smaller bronchial tubes may occur, owing to invasion of saprophytes. This however, is an incident of rare occurrence.

Lastly, we may mention pseudomembranous bronchitis which, when very extensive, may cause death by asphyxia. This may occur notably in diphtheria, as I have pointed out in a previous chapter (p. 177).

The Lungs in Infectious Diseases.

Preliminary Considerations of Normal Physiology. Pulmonary lesions are very frequent in the course of infectious diseases. Some

disseminated râles are commonly heard during life; at the necropsy parenchymatous alterations are almost always disclosed, which are spoken of as congestive phenomena.

The interest of pulmonary lesions appears to be more considerable, as the lungs are charged with more important functions than was once believed. If this organ had nothing else to do than ensure gaseous exchanges and hematosis, even then it would be considered of vital importance. In addition, however, it plays a protective rôle for the entire organism against infections and intoxications. Its action upon microbes has already been described (pp. 156–159). Its action upon poisons is by no means less important, since microbes act by virtue of the toxins they secrete. It had long been known that the lung served as an emunctory for volatile substances. The offensive breath noticed in patients in the course of infections, especially when these are accompanied by excessive intestinal putrefactions, suffices to demonstrate the elimination by the respiratory organs of certain principles—sulphuretted hydrogen, methylamercaptan, ammonia, volatile bases, etc. Modern researches have further demonstrated that the lungs also act upon those substances which they do not eliminate by subjecting them to modifications analogous to those accomplished by the liver. The importance of this fact is evident, since all soluble substances, whatever their mode of entrance may be, must pass through the pulmonary network before reaching the nerve centres.

The action of the lungs upon poisons has received experimental demonstration. The writer experimented with strychnine sulphate[1] and ammonium carbonate; Boeri and Giuranna,[2] and Cafiero[3] experimented with twelve poisons; in all these cases the protective action of the lungs was more or less marked.

We may safely conclude that the lungs act as protective organs against infections and intoxications. It may therefore be asked whether the disturbances observed in the course of infections of the respiratory apparatus are simply due to asphyxia or whether intoxication by pulmonary incompetency occurs as in the case of hepatic incompetency.

[1] Roger. Action des organes sur la strychnine. La Presse Médicale, April 15, 1898. Action des poumon, sur quelques substances toxiques. Ibid., June 7, 1899.

[2] G. Boeri and G. Giuranna. L'azione protettiva del pulmone. La Riforma medica, Dec. 2 and 3, 1899, No. 97.

[3] Cafiero. Recerche exp. sull' azione protettiva del pulmone. Gazetta degli ospedali e delle cliniche, 1899, No. 97.

Respiratory Disorders. The respiratory manifestations occurring in the course of infections may consist simply of functional disturbances of nervous origin or be dependent upon blood alterations. Certain paroxysms of dyspnea observed in the beginning of scarlatina may be connected with these nervous influences. At a more advanced period changes in the respiratory rhythm may characterize certain grave nervous forms or indicate paralysis of the bulbar centres, as in diphtheria, or express some cerebral or meningeal complication. Dyspnea may also be due to blood alteration. Such is notably the case in hemorrhagic variola. The panting respiration is at times the only symptom expressing the gravity of infection. In such cases, while the condition of the skin is serious, the general state often seems to be very satisfactory, and the consciousness of the patient is so perfect as to render it difficult for those around him to believe that he will die within a few hours.

Modifications in the respiratory rhythm, dyspnea or Cheyne-Stokes type of breathing, expressing a renal complication, are likewise due to blood alteration. Such, however, is not always the case. In the course of infectious nephritis dyspnea may often occur as a result of acute pulmonary edema.

Classification of Pulmonary Lesions of Infectious Origin. The lesions attacking the lungs may be divided into three groups, according as the process is one of primary infection, secondary localization of a specific process, or dependent upon ordinary bacteria.

The lungs may be the primary or exclusive seat of a well-determined infection. It is to be noted that while fibrinous pneumonia manifests, by its clinical features and lesions, indisputable autonomy, and seems to be worthy of classification among specific infections, it falls, in view of its microbe, to the rank of non-specific infections. As a matter of fact, the pneumococcus is a quite commonplace agent, capable of giving rise to very different processes, such as bronchitis and bronchopneumonia. In fact, clinical study and anatomico-pathological investigations have thrown down the barriers once established between lobar and lobular pneumonia. These two processes are connected one with the other by a number of transitions, so that pneumonia has somewhat lost its specific character.

The lungs may be attacked by a specific process invading them primarily or secondarily in an exclusive, predominant, or accessory manner. The fact that the respiratory apparatus freely communicates with the exterior explains the easy arrival of morbid germs.

It is hardly necessary to mention the frequency of pulmonary tuberculosis and the possibility of primary infection of the lungs by anthrax and glanders.

Anatomical and functional modifications occurring in the lungs in the course of infectious diseases are more important. Two kinds of lesions develop: some result from the localization of the principal agent; others depend upon an additional infection. Of late the importance and frequency of secondary infections in the lungs have, perhaps, been somewhat exaggerated. Every bronchopneumonia occurring in the course of infections is generally considered as a superadded process. The primary disease is supposed to play simply a predisposing rôle. It is well to remember that the situation is the same as in the case of the throat. The great number of microbes present in the upper parts of the respiratory apparatus which, when the mucous membrane is dried by fever, may be carried down to the deeper parts by the air current, accounts for the frequency of invasions by ordinary microbes. The latter, however, may do no more than play a secondary rôle. An important point must be noted here. These common microbes, being capable of developing more readily, inhibit the development of others in artificial culture media; hence the possibility of errors in interpretation. These considerations are supported by the researches of Dr. Lesage, who believes that bronchopneumonia of measles depends upon the specific microbe of the latter disease. The author has also noticed that in variola the pulmonary foci at times contain very few bacteria, while, on the other hand, large numbers of the special elements which seem to be characteristic of this infection are present.

We are thus led to the question whether lobular pneumonias always result from propagation of the process from the smaller bronchi—*i. e.*, an infection spreading from the bronchial ramifications toward the alveoli. Is it not likely that the lesion is often produced by propagation of the process through the bloodvessels? The pathogenic germs, on arriving through the blood current at the capillaries of the lungs, are arrested there and give rise to an inflammatory process. In fact, when it is remembered that some congestion or even splenization is discovered in almost every necropsy, the endogenic origin of certain infectious processes seems highly probable.

Pulmonary lesions may be divided into six varieties: congestion, splenization, lobular pneumonia, lobar pneumonia, hemorrhage, and gangrene.

The expression *pulmonory congestion* is of too common use to be discarded. It is not, however, an exact expression. Necropsy always reveals more important alterations than the term in question indicates. What is observed is not simply dilatation of the vessels; there are exudates and serous effusions appreciable by the unassisted eye. When the parenchyma is compressed, a frothy and aërated fluid comes out. A certain degree of edema is, therefore, added to congestion. Histological examination confirms this finding, and chemical analysis further demonstrates the presence of an exudate in the alveoli. It is to be remembered, therefore, that some albuminous effusion, more or less rich in cells, is always found. Some of the cells originate from desquamation of the alveoli; others represent various leucocytes.

On examining the lungs of individuals dead of infections, it is often noted that crepitation is not well marked at certain points, particularly in the posterior and lower parts: the lung tissue presents a red color, somewhat bluish or blackish. This condition is designated *splenization*, but the lesion is really more pronounced than this term, adopted in view of the macroscopic appearance, indicates.

Coincidently with the latter lesion, foci of pneumonia are observed. This does not mean that splenization represents the first stage of hepatization. The process is different, and splenization at many points gives way to *hepatization*. The latter is characterized, as is known, by a transformation of the tissue, which becomes dense, airless, red or gray in color, and, at least when it is red, resembles the tissue of the liver. This hepatization takes place in two different ways: Sometimes it affects the lobules individually; at other times collectively. This distinction is expressed by the terms lobular and lobar pneumonia. There is no essential difference between the two processes. The lesions considered in themselves may be identical: they may be equally rich in cells and contain the same amount of fibrin. In true pneumonia, however, all the parts of a lobe are attacked simultaneously, and all present the same stage of evolution, so that on section we obtain a homogeneous slice. In lobular pneumonias, even when they are of pseudolobar type, the lobules are invaded one by one, so that on section we see different appearances: the process is more advanced in some than in other lobules. Moreover, since in most cases all the lobules of a lobe do not participate in the same process, the result is a mixture of complex lesions, so that by the side of foci of hepatization or of a nidus of broncho-

pneumonia, as it is sometimes called, we may see lesions of another order—edema, splenization, or emphysema.

Lobular is far more frequent than lobar pneumonia in the course of infections. The latter may, however, occur in the beginning of the most diverse diseases. The most common association is that of typhoid and pneumonia. These pneumonias, appearing from the start of an infection, occur in individuals capable of reacting in an almost normal manner, and generally run a favorable course, behaving like plain pneumonias. The author observed a case in which pneumonia and scarlet fever appeared simultaneously, and the evolution ran its course in a regular manner. Likewise, during convalescence pneumonias are often benign and present nothing special. On the contrary, during the stationary period pneumonias possess special characters: the beginning frequently escapes observation; the crepitant râle is absent or does not present the classical features: small moist râles only are heard. In other instances the blowing murmur is observed from the first. The reactionary phenomena are variable. At times dyspnea or aggravation of the general state of the patient, as expressed by high temperature, dryness of tongue, and acceleration of the pulse, lead to auscultation of the lungs. Evolution is sometimes extremely rapid; these pneumonias are capable of killing in a few hours. When life is prolonged the focus manifests a tendency to spread and undergo purulent transformation, and invade the pleura. If the patient survives, resolution of the lesions is tedious. In fatal cases necropsy reveals hepatization to be less dry and less rich in fibrin than in cases of plain primary pneumonia.

Lobar and particularly lobular lesions are also liable to invasion by saprophytes and to gangrenous transformation. It must be recognized, however, that pulmonary gangrene has become very rare, if we except those cases in which it is due to disorders of deglutition, as is observed in diphtheritic paralyses.

The last pulmonary manifestation to be observed is *hemorrhage*. This may occur in the form of a circumscribed infarct or a diffuse infiltration. The latter variety is especially frequent in those infections which produce important blood alterations, notably in hemorrhagic variola. It may, however, be encountered under other circumstances. At the necropsy of an individual dead of a malignant scarlatina the author found diffuse hemorrhage in both lungs. He also observed intense congestion in the right and diffuse hemorrhage in the left lung of a man who died on the fourth day of an erysipelas

with progressive asphyxia and high temperature. Circumscribed hemorrhagic foci may also develop as an epiphenomenon in a nidus of bronchopneumonia, or they may result from small emboli sent by the heart or vessels, or, finally, by circumscribed thromboses.

Among these various manifestations lobar and lobular pneumonias are undoubtedly the most frequent. Their frequency varies according to the disease and the age. The author's statistics show, in this connection, that measles stands at the head of the list; next come erysipelas and diphtheria; variola occupied the fourth position. Pulmonary complications are altogether exceptional in scarlatina and varicella.

The influence of age may be seen if all the observations of the author are put together regardless of disease. The patients are divided into three groups with regard to age: (1) First childhood—*i. e.*, below two years of age; (2) second childhood—*i. e.*, from two to fifteen years of age; (3) above fifteen years of age. It is thus found that pulmonary complications are thirty times less frequent for the same diseases in adults than in children below two years of age. This can be seen from the following table:

	Number of Observations.	*Cases with Pulmonary Lesions.*	*Fatal Cases.*	*Percentage.* *Morbidity.*	*Mortality.*
First childhood .	613	134	70	21.9	11.4
Second childhood	974	67	17	6.9	1.7
Adults . . .	6445	48	33	0.7	0.5
Total . .	8032	249	120	3.1	1.4

The author's observations further show that pulmonary complications do not occur with the same frequency, as regards the age, in the various diseases under consideration. Here is the result of our statistics:

Classification of Infections in the Order of Decreasing Frequency of Pulmonary Complications.

First Childhood.		*Second Childhood.*		*Adults.*	
Measles,	31.0 per cent.	Diphtheria,	22.2 per cent.	Erysipelas,	6.2 per cent.
Diphtheria,	28.5 "	Measles,	20.7 "	Variola,	2.3 "
Scarlatina,	10.7 "	Variola,	3.2 "	Diphtheria,	0.9 "
Erysipelas,	9.0 "	Scarlatina,	1.3 "	Measles,	0.6 "
Variola,	9.3 "	Erysipelas,	0.0 "	Scarlatina,	0.2 "
Varicella,	1.0 "	Varicella,	0.0 "	Varicella,	0.0 "

When the relative mortality in pneumonia is examined an unexpected fact is met with, namely, that bronchopneumonia of measles

is the complication most often curable. Finally, if we consider gravity according to age, we see that, in the majority of infections, recovery is most frequent during second childhood. Adults are seldom attacked, but when they are the prognosis is very unfavorable, since the mortality varies from 50 to 75 per cent. The following summary shows the facts in this respect:

	Percentage of Mortality in Pulmonary Infections.
First childhood	52.2
Second childhood	25.3
Adults	68.7

Thus an adult attacked by bronchopneumonia has less chance of recovery than a child under two years of age.

Pleuritic Lesions in Infections. When there is a septic or nonseptic lesion in neighboring parts, and notably the lungs, the pleura readily reacts; hence the frequency of pleurisies in the course of various infections. Inflammation in this serous membrane may be expressed by the production of fibrinous exudate, thickening, or pseudomembranes. Dry pleurisies represent a defensive process which often circumscribes the pulmonary lesion and in certain instances prevents rupture of the lung. When inflammation is intense, effusion takes place, which effusion may be serous, purulent, putrid, or hemorrhagic, according to the state of the subject and the nature of the pathogenic agent.

Serous Pleurisies. Serous pleurisy often develops in the absence of any appreciable pulmonary manifestation. It has long been the general belief, therefore, that it may be produced by such common causes as cold. Since the contributions of Landouzy, Kelsch, Kiener, Chauffard, and Gombault, and on clinical as well as anatomico-pathological and experimental grounds, pleurisies from cold are rejected, and the general opinion is that any pleurisy which cannot be accounted for must be considered suspicious, as it is almost always dependent upon tuberculosis. The author says *almost* always, as it is conceivable that it may be caused by some other infection or by a pulmonary alteration escaping observation. This restriction, however, does not lessen the importance of tuberculosis in the genesis of apparently primary pleurisies. The importance of the pleurisy may be so great as to relegate the pulmonary lesion which has caused it to the background, and, as the pleuritic inflammation may resolve and disappear, the physician naturally hesitates to admit the tubercular nature of such a benign process. It is even probable that

serous pleurisy represents a favorable reaction and promotes recovery. The best treatment of a diseased organ is, indeed, to impose upon it perfect rest. By compressing the lung, by preventing its expansion, by immobilizing it more or less completely, pleurisy diminishes its activity, and thus realizes the major indication discovered by therapeutists. There is, therefore, a growing tendency to respect effusions. Barring those cases in which the effusion becomes dangerous by reason of its too great amount, puncture is to be avoided. Thoracentesis is indicated at a later period when there is reason to believe that the acute tubercular attack which caused it is overcome. When the exudate of serous pleurisies is examined, no microbe is generally detected. It may be assumed that the microbes are localized in the diseased membrane or that pleurisy is due to the action of toxins secreted in the pulmonary foci. In some instances examination of the effusion reveals the presence of bacteria and even pyogenics. As a rule, these are few in number, and the fluid must be submitted to centrifugation in order to detect them. Under these conditions, streptococci may be found which, being probably attenuated by the germicidal power of the effusion, have not been able to give rise to a suppurative process.

Pneumonia is admitted to be the most frequent cause of serous pleurisy. The effusion is produced during the stationary period or convalescence. Acute articular rheumatism is given the second place; then come eruptive fevers, typhoid, influenza, and whooping-cough. Serous pleurisy has also been observed in septicemias, pyemias, and even in the course of gonorrhea. It may safely be assumed that in all such cases the pleural effusion is caused by a pulmonary lesion which is too small to be appreciated or is masked by the pleural lesion. Serous pleurisy, however, is not of frequent occurrence in any of the infections above mentioned, except typhoid fever. If reference is made to the author's statistics, but four cases of serous pleurisy are found. During convalescence from variola, measles, scarlatina, and erysipelas patients developed fever and complained of pain in the side. Auscultation revealed the presence of pleural effusion, the serous nature of which was verified by an exploratory puncture. In all four cases recovery was effected spontaneously within ten days. Inoculations with these exudates was not practised; it is, therefore, an open question whether the effusions depended upon latent tuberculosis, the acute infection having played simply the rôle of an incidental cause.

Purulent Pleurisies. After the details given in treating of suppuration (p. 222), the author will not dwell upon the history of purulent pleurisies. They develop under the same conditions as serous pleurisies, and are connected with these by a series of transitions. These two processes are not distinct. Although in most cases pleurisy is purulent from the beginning, it is not rare to see a primarily serous effusion become purulent. Slight modifications in the virulence of pathogenic agents suffice to account for the differences in the process.

Purulent pleurisy may occur in the course of various pneumonias and aggravate prognosis. A certain amount of pus is often found in the pleura, whether the case be one of ordinary pneumonia or a secondary one complicating measles, variola, or erysipelas.

Purulent pleurisy as an affection apparently independent of a pulmonary lesion is not of frequent occurrence. The author has observed several such cases. One occurred in a woman profoundly infected by gonorrhea; she developed a seropurulent pleurisy which was spontaneously cured in a month.

Hemorrhagic Pleurisies. As gangrenous and putrid pleurisies have already been referred to (p. 240) the author's intention is here to say a few words with reference to hemorrhagic pleurisies. This variety of effusion when not dependent upon cancer is generally due to rapid tuberculosis. It is at times observed in pneumonia and bronchopneumonias; it may occur in the most varied infections, as a result of infectious infarcts (Ehrlich), but in the majority of instances it is a complication of typhoid fever. The author does not refer to bloody effusions observed in hemorrhagic infections; these are cases of hemothorax, not of pleurisies.

In typhoid fever the effusion may be sero-hemorrhagic. A similar effusion may occur in pleurisies of convalescence. There are also pleurisies with Eberth's bacillus which appear independently of typhoid fever. The author has reported such a case studied in conjunction with Dr. Charrin.[1] A similar case was published by Kelsch.

Tracheobronchial Adenopathies. The various lesions of the respiratory apparatus readily influence the tracheobronchial ganglia. At the necropsy of individuals dead of pulmonary affections, especially in the case of children, these glands are found enlarged, red, and inflamed. These acute glandular inflammations commonly subside with gratifying rapidity. They persist, however, in certain instances,

[1] Charrin and Roger. Présence du bacille d'Eberth dans un épanchement pleural hémorrhagique. Soc. médicale des hôpitaux, April 17, 1891.

and explain the cough resembling that of whooping-cough occurring consecutively to measles, typhoid fever, and particularly influenza.

In the absence of pulmonary lesions, some infections may cause hypertrophy of the tracheobronchial glands. Whooping-cough is quite notable in this connection. It has also been asserted that, owing to lymphatic anastomoses, anginas and erysipelas of the face may produce enlargement of these glands.

Since the works of Loomis and Pizzini a new problem confronts us. Koch's bacillus is often found in apparently healthy tracheobronchial glands in individuals presenting no trace of tuberculosis. Kalbe has verified this fact and estimates at 8 per cent. the proportion of glands which, though seemingly sound, contain the bacillus. The tubercle germ thus remains inoffensive until an intercurrent disease diminishes the resistance of the organism. The infections which easily affect the bronchial glands are those most capable of thus giving rise to an attack of tuberculosis. It is therefore readily conceivable that whooping-cough and measles play a notable rôle in this connection.

Remote Consequences of Infectious Lesions of the Respiratory Apparatus. As is the case in lesions of other parts of the organism, so those of the respiratory apparatus may be completely cured. When, however, they are profound or repeated, these lesions are often followed by irremediable alterations. Emphysema of an almost incurable character and even splenization are often observed after a bronchopneumonia. The author is therefore inclined to refer to lesions of early age the pulmonary emphysema so frequently observed in adult and advanced age.

As in other parts, cicatrization of lesions may give rise to sclerosis. When the lung is involved in the process the alveolar walls and vascular ramifications are thickened. The same lesion is observed in the pleura, which becomes thickened at certain points, or its two layers may be adherent to each other. Finally, sclerotic lesions may increase emphysema and at times cause bronchial dilatations.

It is thus possible to connect various chronic lesions which frequently coexist and seem to be the remote results of changes arising from infections.

CHAPTER XVI.

INFLUENCE OF INFECTIONS UPON THE VARIOUS PARTS OF THE ORGANISM (*Concluded*).

Buccopharyngeal Manifestations in Measles. Buccopharyngeal Manifestations in Scarlatina. Buccopharyngeal Manifestations of Varicella and Variola. Buccopharyngeal Manifestations in Various Infections. Stomach Disturbances and Lesions of the Intestine in Infections. Amebic Dysentery and Bacterial Dysentery. Choleriform and Dysenteriform Enterites. Choleriform Gastroenterites and Seasonal Diarrheas. Dysenteriform Enterites. Influence of Infectious Diseases upon the Liver. General Characters of the Infected Liver. Semiology of the Infected Liver. Action of Infections upon the Pancreas. Influence of Infections upon the Kidneys. Influence of Infections upon the Genital Organs. Influence of Infections upon Menstruation. Influence of Infections upon Pregnancy. Suckling by Infected Women.

Influence of Infections upon the Digestive Apparatus.

In examining a patient the physician generally does not overlook the condition of the tongue. This inquiry is particularly important in infectious diseases, as it may give diagnostic and prognostic indications of considerable value. A tongue which is excoriated on the borders is a good sign of typhoid fever; an opaline or porcelain tongue is quite peculiar to influenza; the red, raspberry-like tongue is observed especially in scarlatina. From a prognostic standpoint the importance of moisture or dryness of the tongue is well known. When this organ manifests a slight trembling extending to the lips and rendering speech jerky it indicates the imminence of delirium tremens.

Lesions of the mouth and throat are extremely frequent in the course of infectious diseases; but their study is difficult, and the differentiial characters ascribed to them are not very certain. Even bacteriological examination is not free from considerable difficulties and not infrequently leads to errors. In fact, the buccal cavity is widely open, and even under normal conditions is inhabited by multitudes of microbes. Microscopic examination and cultivation always reveal bacterial associations (p. 145).

It has, however, been possible to determine certain clinical types corresponding to a bacteriological formula. In the first place, diph-

theria is such a type; then buccopharyngeal localizations of general infectious diseases: the eruptive fevers, syphilis, and tuberculosis give rise to well-determined buccal lesions. In some instances differentiation is based upon clinical observation, and, therefore, it is possible to doubt its value. Such, for instance, is the case in scarlatinal angina, which is considered by some authorities as an enanthema produced by the scarlatinal virus, by others as a common inflammation due to the streptococcus. This constant intervention of the streptococcus in all buccopharyngeal inflammations further complicates the question. Hence, as was indicated by Dr. Lemoine, when the rôle of this agent is to be determined, it is necessary to look for it in the deeper parts of the tissues; for example, by puncturing the tonsils, since if one is contented with buccopharyngeal exudates, one may obtain a virulent streptococcus without having any right to draw a conclusion from this experiment. In fact, it has been demonstrated that certain germs are exalted in the course of various diseases, which is particularly true as regards the microbes of the mouth, and notably the streptococcus. We are thus able to explain certain facts which would otherwise appear very strange. For example, the saliva of a scarlatinal patient expelled into the physician's face is known to have produced erysipelas. The author has observed a great number of simple sore throats contracted by individuals nursing scarlatina cases. Finally, what seems to be more demonstrative is the fact that parents whose children suffered from diphtheria contracted at their bedsides erythematous or exudative anginas in which Loeffler's bacillus could not be detected. This fact suffices to show that the diphtheritic microbe may favor exaltation of the ordinary bacteria which, in their turn, produce by contagion sore throats among those surrounding the patient.

Buccopharyngeal Manifestations in Measles. In measles an enanthema analogous to the cutaneous eruption is observed in the palate. Like the latter, it appears in the form of small discrete spots of an intense red color. Certain symptoms observable in the mouth enable the physician to make an early diagnosis. Such is erythematous-pultaceous gingivitis, to which Comby has drawn special attention: a white coating, which is formed of desquamated epithelial cells, and may readily be wiped out by slight friction, is seen upon the gums. This manifestation is perfectly plain; it remains to be seen whether it is specific. More value is attached to Koplik's sign, which is appreciable as early as the first or second day of invasion, and disap-

pears when the cutaneous eruption appears. The sign consists in small, bluish-white, slightly elevated spots, surrounded by a red circle, and varying in size from 1 mm. to 5 mm. (0.04 to 0.2 inches). and in number from five to twenty. These appear upon the mucous membrane of the lips, tongue, and inner surface of the cheeks between the labial commissure and the opening of Stenon's duct. These productions are formed of fatty epithelial cells, resist friction, but can be removed by means of forceps.

These various manifestations should not be mistaken for inflammatory processes; they are simple enanthemata.

Among buccal manifestations we must note angina, which may be observed during the invasion of measles. It is a complication of exceptional occurrences, at least in adults. It may also be observed during convalescence. The author has observed twenty-six such cases. It is generally an erythematous, seldom a pultaceous, angina.

Buccopharyngeal Manifestations in Scarlatina. As is known, buccopharyngeal manifestations are far more frequent in scarlatina than in measles. The angina is the initial phenomenon, and is never absent. There are two principal hypotheses as to its nature: the buccopharyngeal symptoms may be considered as a simple enanthema, or it may be held to be a true angina due to the microbe of scarlatina. To the former opinion it may be objected that the inflammatory phenomena are too intense and that, while a patient suffering from measles does not say anything regarding his throat, a scarlatinal patient first complains of pain in deglutition. This objection can readily be answered by the statement that scarlatinal enanthema is more intense; the difference is one of degree, not of nature. It produces alteration in the epithelium, and thus permits buccal germs to cause further injury in the mucous membrane. It is also to be noted that in certain cases of scarlatina angina is mild and the patient suffers little; there are a great many intermediate degrees between the mildest and the severest manifestations.

The other parts of the mouth are little affected, except the tongue, which is involved in the eruptive process. From the third to the sixth day the epithelium of the tongue is desquamated, and the organ assumes a characteristic appearance comparable to that of a strawberry. It is not a glossitis, since the patient does not experience any pain or any functional trouble. It is simply a process of desquamation similar to that of the skin, and its early occurrence in the tongue is explained by the moisture of the region.

The greater intensity of the scarlatinal exanthema explains the frequency of secondary buccopharyngeal infections. The buccal streptococcus is exalted and produces various alterations which appear simultaneously with the specific angina, or a few days later, and at times only during convalescence.

In scarlatina, as in measles, angina may assume a gangrenous character. This evolution occurred in two of the author's cases—children; one of them thirteen months and the other three months old, and both succumbed. The uvula and tonsils were completely sphacelated in both instances. Cultivation from the lesions revealed the presence of streptococcus, staphylococcus, and a non-virulent anaërobic microbe.

Buccopharyngeal Manifestations of Varicella and Variola. Varicella and variola may also give rise to buccopharyngeal phenomena. Here, however, the question is not one of erythema; vesicles and pustules appear just as in the skin. The eruption is generally scanty in varicella, and is produced in all parts of the mouth without distinction—cheeks, palate, tongue, and gums. Variolar eruption is of greater importance. It sometimes appears early, and may then serve as a diagnostic guide. When it appears at the same time as the cutaneous eruption it evolves more rapidly, and thus, in doubtful cases, when the diagnosis between measles and variola is undecided, examination of the throat removes all doubt: papules and vesicopustules are seen occupying the palate, uvula, pillars, gum, tongue, and cheeks. This eruption is very copious in coherent and confluent variolas and causes dysphagia from the sixth or seventh day; it may then aggravate prognosis considerably by disturbing alimentation.[1]

Buccopharyngeal Manifestations in Various Infections. We might review all infectious diseases, since all may affect the buccal cavity. Angina is frequently observed in typhoid fever, in which its appearance is quite variable, being sometimes pultaceous, at times ulcerative, and in other instances gangrenous. It is generally admitted that erysipelas frequently begins with throat symptoms. This classical opinion seems to the author inexact. It must be due to the fact that patients generally speak of sore throat when they suffer from painful enlargement of the lymphatic glands often accompanying the cutaneous lesions, and sometimes preceding them by a day or two. In two instances they existed four days before the

[1] Coste. Quelques considérations sur le diagnostic, le pronostic et le traitement de la variole. Marseille méd., January, 1898.

appearance of erysipelas. In some cases, however, erysipelatous angina does occur. In twenty of the author's cases it announced the onset of the disease. In a youth of fifteen years of age erysipelatous inflammation started from the tongue, which was highly swollen and very painful and presented a couple of bullæ which soon opened and gave issue to a sanguinolent discharge.

Stomach.

Numerous observations have proved the involvement of the stomach in infectious processes. The gastric disturbances may theoretically be classed in four groups according as they are of nervous, muscular, chemical, or microbic origin. Unfortunately, accurate investigations are lacking and are very difficult. Gastric chemism can hardly be studied in the course of acute infections. In view, however, of the coated condition of the mouth, the disgust experienced by patients for food, and frequent vomiting of undigested aliments it may safely be assumed that the digestive secretions no longer possess their normal characters. At any rate, it is in nowise to be wondered at that gastric secretion is also disturbed when all the other secretions are. Moreover, chronic gastritis so often follows the evolution of acute diseases that it seems perfectly rational to assume a causal relation between the two processes.

As in many other visceral disturbances, vomiting is often of nervous origin. We refer particularly to vomiting at the onset of infections. It occurs soon after the initial chill, and accompanies the first symptoms. At this stage of evolution gastric alterations cannot be supposed to have taken place, and, in fact, the vomiting is a transitory incident. It is often observed in the beginning of scarlatina, measles, and erysipelas. In the latter disease it sometimes represents the first symptom of a relapse. Special mention must be made of the initial vomiting in variola, occurring for twenty-four or forty-eight hours coincidently with extremely intense pain in the epigastrium; its diagnostic value is no less important than that of rachialgia.

Vomiting during the stationary period and convalescence express, on the contrary, gastric alteration. Hence they are more persistent and have an unfavorable prognostic significance. It is to be acknowledged, however, that they are not very frequently observed, and it is surprising to see patients overcome their dislike for nourishment and digest their food so well. It has thus been possible to feed

typhoid cases. In the author's wards variolar patients receive relatively abundant nourishment without any inconvenience.

Observations by Kalmus, Hayem, Lion, and others demonstrate the possibility of an invasion of the gastric glands by microbes. Gastric ulcerations of typhoid fever have long been known. Dieulafoy's observations proved the gastric localization of the pneumococcus. The same observer has called attention to hematemesis occurring in the course or at the end of an appendicitis or internal strangulation. Having in several instances opened the stomach of individuals dead of variola, the author has sometimes found erosions which are at times quite profound. Diffuse bloody infiltration with numerous ulcerations may be found in cases of hemorrhagic variola, explaining the occurrence of hematemesis during life.

These facts, which enable us to understand the mechanism of acute gastric phenomena in the course of infections, may be cited in support of the opinion that chronic ulcerations, notably simple ulcers, are of microbic origin. The process is less intense and more slow than in the case of acute disorders, and the lesion insidiously formed gives rise to symptoms long after the termination of the infectious malady of which it is a remote consequence.

Primary or predominant attacks by general specific infections are rarer in the stomach than in other organs. Anthrax, tuberculosis, and syphilis of the stomach are but exceptionally observed. In rare cases phlegmonous gastritis may occur as a primary or a secondary manifestation in pyemia, and, according to observations of Ziegler, Mintz, and Derbek, seems to be due to the streptococcus.

Disturbances and Lesions of the Intestine in Infections.

Almost all infectious diseases produce intestinal disturbances. The latter, like those of the stomach, may be of nervous, muscular, chemical, or bacterial origin. The influence of bacterial action is considerable; numerous researches have demonstrated that intestinal microbes, notably the colon bacillus, become virulent in the course of infections. This fact has a double interest. When a highly virulent bacillus is found in the intestine the disturbances observed may be erroneously attributed to its action. On the other hand, the increased activity of the intestinal germs accounts for certain local symptoms, such as tympanites—perhaps favored by temporary atony of the muscular fibers—diarrhea, and even certain general manifestations, some kind of secondary digestive autointoxication.

This constant participation of the intestine in infectious processes explains the development of chronic conditions: some individuals continue to suffer from certain intestinal disorders, notably from a tendency to diarrhea, on the slightest dietetic error or cold; others suffer from rebellious constipation. The author has observed several instances of mucomembranous enteritis.

We are thus led to the question whether or not infections play a rôle in the development of appendicitis. This theory seems plausible. The frequency of follicular lesions of the intestine give it some support, but facts hardly respond to what is expected. Only once in our wards has the author seen appendicitis follow measles. On the other hand, having examined a certain number of appendices at the necropsy of individuals dead of various infections, particularly variola, the author has detected no lesions. The importance of these negative results should not be exaggerated, however. More numerous investigations are required in order to determine the value of the theory which is perfectly consonant with the data of general pathology.

As already stated, intestinal functions seldom remain regular in the course of infectious diseases. Sometimes constipation predominates, as is the case in erysipelas; at other times, diarrhea which, by reason of its too great severity, may prove fatal. Some authors have described an intestinal form of scarlatina characterized by profuse and incessant evacuations. As a rule, intense and generally bilious diarrhea is observed in the beginning of measles; it seems to be dependent upon an intestinal enanthema. At a more advanced period choleriform or dysenteriform diarrheas may appear which, next to bronchopneumonia, represent the gravest complications of the disease. This complication is particularly dangerous in the case of children. The author has, nevertheless, observed the case of an adult who, at the end of measles, succumbed to putrid pleurisy of intestinal origin.

Even in a benign disease, such as varicella, intestinal disorders may prove fatal in young children. It is, however, in variola that this complication is of particular importance. Trousseau laid stress upon the diarrhea of the invasion period, which ceases as soon as the eruption appears. While constipation is the rule in slight cases during the stationary period, diarrhea renders the prognosis unfavorable in serious cases. It is a fetid and profuse diarrhea, resisting most medicaments, and is hardly checked by astringents and notably

by preparations containing tannin. In hemorrhagic variola bloody stools are frequent. In certain cases, especially toward the end of the stationary period, the stools may contain a certain amount of blood; this is a complication of importance, but does not render prognosis particularly bad. In fact, the author's observations show that of all visceral hemorrhages enterorrhagia, when alone, is the least grave.

It is not necessary to describe the intestinal localizations of specific diseases. As in the case of the stomach, localization of anthrax, tuberculosis, syphilis, and actinomycosis may also occur in the intestine. Tuberculosis of the stomach is an event of very rare occurrence, while it is quite frequent in the intestine, where it may assume the most varied forms.

Amebic Dysentery and Bacterial Dysentery. In the classification of infectious diseases (pp. 24–30) it was stated that two principal infections localize themselves in the alimentary canal, viz., cholera and dysentery. Typhoid fever, when classed with septicemias, might also be included in this group; leaving it aside, however, the author will consider only cholera and dysentery. The specific nature of the former disease has been demonstrated by clinical observation and epidemiology, as well as by Koch's discovery. The author must expand at some length upon dysentery. Most clinicians hold it to be a disease perfectly defined and possessing full autonomy. Bacteriological investigations, however, seem to lead to a quite different conclusion.

Certain authorities attribute dysentery to amebæ. Numerous observations reported by Kartulis seem to be convincing. Recent researches of Marchoux demonstrate that amebæ may produce in cats a disease analogous to dysentery and even induce hepatic abscesses. This experimental result confirms those observations in which protozoa only, in the absence of all bacteria, were found in the pus of dysenteric abscesses of the liver.

Numerous observations have been recorded in which amebæ were not found. On the other hand, bacteriologists have described various bacteria detected in cases of dysentery. Some have noted special microbes of the bacillary form (Ziegler, Babes, Ogata), or presenting the appearance of diplococci (Silvestre); others have met with bacteria which were already known, such as the streptococcus, bacillus pyocyaneus, and proteus vulgaris. The majority of authorities, however, have isolated bacilli related to the colon bacillus or

occupying an intermediate position between the latter and the typhoid bacillus; it will suffice to cite the names of Klebs, Chantemesse, Widal, Grigorieff, Laveran, Arnaud, and especially Celli and Shiga, who have recorded highly interesting researches on this subject.

Experimenting with dysenteric dejecta kindly sent him by confrères practising in countries where the disease is endemic, the author found no amebæ in any instance, but a bacillus resembling the ordinary bacillus coli. It readily developed in bouillon, to which it imparted a very disagreeable putrid odor. Agar-agar was covered by a viscid, thick layer; gelatin was not liquefied, but small gaseous bullæ were at times seen in its deeper parts; milk was generally coagulated within forty-eight hours, and the medium became acid. On potatoes a yellowish culture was obtained.

What right have we to conclude that this bacillus is the cause of the disease? Have we not in the presence of the ordinary colon bacillus, a constant resident of the human intestine? The question is certainly difficult of solution. In favor of the pathogenic rôle of this bacterium its action upon animals may be advanced, which action varies according to the degree of gravity of symptoms observed in man. Another argument in support of the pathogenic rôle of this microbe is based upon the fact that it produces extremely powerful toxins in culture media. The sterilized cultures when injected into the veins of rabbits cause diarrhea which at times is so severe as to be almost a continuous flow. These facts suffice to establish the individuality of the dysenteric colon bacillus. Another fact which imparts to it a particular feature and conclusively shows its pathogenic rôle in man is that the serum of patients convalescent from dysentery agglutinates the dysenteric colon bacillus, but does not agglutinate the ordinary colon bacillus. This was noticed by the author and by Celli and Shiga. Flexner[1] has obtained agglutination with the serum of patients suffering from bacterial dysentery, while the result has been negative in the case of amebic dysentery. The history of dysentery is, therefore, to be divided into two.

Choleriform and Dysenteriform Enterites. Alongside of the specific intestinal infections spoken of above are to be placed common infections which simulate them.

Choleriform gastroenteritis, which has long been known, resembles

[1] Flexner. On the Etiology of Tropical Dysentery. Bulletin of the Johns Hopkins Hospital, October, 1900.

genuine cholera by its symptoms. Distinction between the two has been based upon epidemiological data. Bacteriology has demonstrated the absence of the comma bacillus in such cases, of which numerous examples are every year observed during the hot season, even in temperate climates. Likewise, dysenteriform enterites are met with in the form of small epidemics. The stools contain no amebæ, but a bacillus distinctly different from the dysenteric colon bacillus above described.

The fact that such analogous manifestations are produced by different parasites is not to be wondered at. It is well known that certain poisonings are expressed by symptoms similar to those of cholera; such, for instance, is the case in poisoning by tartar emetic. On the other hand, intoxication by corrosive sublimate gives rise to lesions and symptoms comparable to those of dysentery. Clinical observation is not yet sufficient to give us an accurate idea of the nature of all these acute enterites; it does not yet enable us to trace them with certainty to their cause, to determine the infectious agents responsible for their development, or even to discern with precision infections from toxic manifestations. These remarks are equally applicable to cholera and dysentery. Hence it seems to me that the present task of the clinician is to determine and describe the differential characters which will lead to definite distinction of the diverse forms of dysentery and to concordance of clinical observations with bacteriological findings.

Choleriform Gastroenteritis and Seasonal Diarrheas. Seasonal diarrheas may assume either choleriform or dysenteriform characters.

The frequency of choleriform diarrhea varies somewhat from one year to another, as may be seen from the following figures:

Year.	*January.*	*February.*	*March.*	*April.*	*May.*	*June.*	*July.*	*August.*	*September.*	*October.*	*November.*	*December.*	*Total.*
1896	..	..	2	..	2	3	4	6	1	..	..	..	18
1897	..	..	..	..	1	4	10	5	..	..	..	..	20
1898	..	..	..	..	..	3	2	20	24	1	1	1	52
1899	..	4	..	2	..	2	9	19	7	..	..	..	43
1900	..	..	..	1	..	1	6	10	5	3	..	1	27
Total	..	4	2	3	3	13	31	60	37	4	1	2	160

Seasonal influence, although undoubted, is not always the same. Some cases are at times met with during the cold season. The greatest number, however, occur in August. This is indicated by

my statistics, but fully shown by those of the French army. It may be seen therein, for example, that the monthly morbidity of diarrhea amounts to 750 cases in June, 1350 in July, reaches 1700 in August, and falls to 1000 or 1100 during the following month.

The influence of heat, ingestion of fruits and ice water do not suffice to explain the genesis of the phenomena. The rôle of water must first be taken into account. The noxous influence of the latter was recognized by ancient observers, particularly by Hippocrates, and has been demonstrated by numerous contributions of recent period. It has thus been learned that epidemics of diarrhea sometimes coincide with those of catarrhal icterus, typhoid, and malarial fevers. In Paris diarrhea and typhoid regularly appear when, in summer, Seine water is drunk instead of spring water. It should not be concluded, however, that alterations in water suffice of themselves to account for the frequency of seasonal diarrhea. Heat seems to disturb the functions of the intestine and hinder the secretion of ferments; it leads to drinking of considerable quantities of liquids which dilute and weaken the digestive juices. Moreover, aliments are more readily altered and fermented in the hot season. Lastly, a part is played by overexertion, as is so frequently observed among soldiers during fall maneuvers and in the time of war.

Unlike genuine cholera, diarrheas, even when assuming choleriform appearance, do not seem to be due to a specific agent. The opinion is gaining ground that the colon bacillus is the principal agent concerned. This microbe acts by secreting toxic substances in the alimentary canal, and thus gives rise to the development of morbid manifestations. The principal poison contained in the stools was found by Dr. Robert, who pursued researches in our laboratory, to be a substance which is precipitated by alcohol. Its injection into the rabbit causes diarrhea, hypothermia, myosis, and at times nystagmus and convulsions. If the animal recovers, hypothermia is followed by hyperthermia, which may be considered as a reaction of the organism. These results, when compared with those obtained by the employment of sterilized cultures of the colon bacillus, lead us to the conviction that the symptoms of gastroenteritis may readily be explained by the theory of intoxication. Some authorities hold dehydration responsible for cramps. This interpretation is not plausible, since the intensity of cramps is related to the gravity of the phenomena rather than to the amount of alvine evacuations. Moreover, cramps may appear with the first stools,

and may at times precede them. When the general condition is improved, cramps disappear, while diarrhea still continues.

The toxins are rejected by means of vomiting and diarrhea, which represent reactionary phenomena designed for the elimination of the poisons. Hence, administration of a purgative and lavage of the stomach often relieve the disturbances by completing nature's task.

Among the organs affected the liver must first be mentioned. In one-eighth of the cases this gland is enlarged and often painful on palpation. The liver must struggle against the toxins and protect the organism; but it is often injured in its resistance, for this organ is constantly found degenerated at the necropsy. The kidneys are seldom involved, albuminuria is quite rare, which I have observed only in one-seventh of the cases.

The mortality from seasonal gastroenteritis is not very high. Out of a total of 160 patients we lost 14 (8.7 per cent.). In most cases death occurs at the end of three or four days. In certain instances, however, it supervenes speedily. Thus, a young man, twenty-three years of age, was taken sick on August 26, 1899, at 6 A.M., with fetid diarrhea and vomiting. He was brought to the hospital on the same day at 4 P.M. The face was cyanosed, the extremities cold and blue, the pulse thready, the patient unconscious with a central temperature at 105.1° F. (40.6° C.). In spite of injections of caffein and of artificial serum he succumbed an hour later, less than twelve hours after the onset of the attack. At the necropsy intense congestion of the intestines, prominence of Peyer's patches, and dilatation of the right heart were the only alterations discovered.

Dysenteriform Enteritis. Dysenteriform enteritis is observed, especially in children, and is not as frequent as choleriform enteritis. Their isolation is not thought to be as necessary as that of persons suffering from the choleriform disease; we, therefore, observed only seven cases in 1899 and two in 1900.

The author undertook some bacteriological investigations upon his patients.[1] Information furnished by direct examination is generally of little importance. In no instance have I found amebæ. On the other hand, the microscope revealed a more or less marked number of microbes, some of which were round, others in the form of rods.

[1] Roger. Recherches bacteriologiques sur l'entérite dysentériforme. Presse médicale, January 3, 1900.

In slight cases the microbic forms were quite numerous. In grave cases one type predominated, viz., a quite large rod, resembling by its form and size the bacillus of anthrax, but differing from it by its rounded extremities. It measured 5μ to 6μ in length and 1.3μ or 1.5μ in breadth. The cultures prepared with the mucus of the dysenteriform discharges likewise revealed numerous microbic varieties in slight cases and predominance of certain bacilli in grave ones.

In the presence of these microbic varieties no definite conclusion could be drawn. I therefore resorted to the method of inoculation

Fig. 36.



Bouillon culture of bacilli found in dysenteriform enteritis (five hours old).

of the cultures into animals. After a sojourn of twenty-four hours in the incubator the bouillon sown with intestinal mucus was injected into rabbits by the intravenous route in the dose of half a cubic centimeter. All the animals succumbed, most of them in less than twenty-four hours. When a small drop of blood was examined under the microscope a variable number of bacilli were seen which were at times slightly encapsulated. It would seem as if the animal had died of anthrax. In fact, the bacilli are quite large. They measure in the blood from 5μ to 6μ in length and 1.3μ to 1.5μ in breadth. These microbes, however, can readily be distinguished from the bacillus anthracis by the following characters: They

are not as long, and are at times so short as to be liable to be mistaken for micrococci; they are decolorized by Gram's method and rounded at their extremities; finally, some present a constriction at their middle part; in the latter instance the extremities are oval, hence the appearance is that of a diplococcus. When the bacillus divides at the constricted point each part simulates a micrococcus; but these newly formed elements soon become elongated and assume the characteristic form.

Cultures succeed in all of the usual nutrient media. For instance, a bouillon culture becomes turbid at the end of four or five hours.

FIG. 37.



Same culture (forty-eight hours old).

If it is examined at that time (Fig. 36) numerous rods measuring 4μ to 6μ in length and 1μ in breadth are found; others are in pairs measuring 3μ to 3.5μ by 1μ. On the following days (Fig. 37) the microbes are more slender and measure mostly 2μ or 3μ by 0.8μ.

Culture on vegetables has a different appearance. (Fig. 38.)

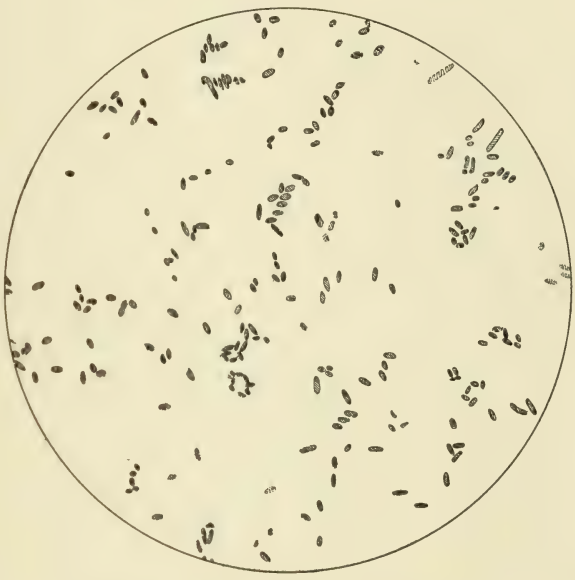
The bacilli are more slender and generally shorter and mixed with oval elements, often agglutinated by a viscid substance which renders staining very difficult. The elements measure 0.75μ to 1μ in length, 1.25μ to 0.5μ in breadth.

This bacillus is motile, stains readily, but is decolorized by Gram's method. The results obtained upon animals show that it possesses

a marked predilection for the large intestine; even when injected through the veins it localizes itself in the terminal parts of the digestive tract.

The liver exercises a destructive action upon this bacillus when the culture is very young—*i. e.*, while it contains very little, if any, toxin. Animals inoculated under these conditions through the portal vein readily withstand doses which are fatal when injected by the peripheral veins. In most instances destruction of the bacilli is complete. In two cases, however, their presence induced hepatic abscesses. The pyogenic properties at times manifested by

FIG. 38.



Culture on carrot (twenty-four hours old).

this microbe explain this result; it is to be noted, however, that this is not an event of common occurrence. Having injected various pyogenic microbes, such as the staphylococcus aureus, streptococcus, and colon bacillus, into thirty-three rabbits by the portal vein, I have in no case obtained similar results.

In view of the constant presence of the microbe in the cases examined by me and the effects produced upon animals, I am inclined to consider it as the cause of dysenteriform enteritis. This opinion is further supported by the fact that I have not been able to find the same agent in the stools of healthy individuals or of patients suffering from choleriform enteritis.

It may, therefore, be asked whether my microbe represents a new species. In examining the numerous works published on dysentery I have found but two bacteria which may be compared with mine. One of them is described by Ogata; the other, which has several times been encountered in dysentery, is identified with *proteus vulgaris.*

Ogata's bacillus[1] is pathogenic for the mouse, the guinea-pig, and the cat; like mine, it liquefies gelatin. It differs clearly, however, in that it stains by Gram's method. Its morphology is not identical;

FIG. 39.



Proteus vulgaris. Culture upon carrot (twenty-four hours old).

the author describes it as a slender rod comparable to the tubercle bacillus.

As regards the proteus vulgaris, it has frequently been met with in patients suffering from gastroenteritis or even dysentery. The morphological and biological characters are not identical; there are, nevertheless, some obvious analogies—liquefaction of gelatin, fetid odor, same action upon milk, glucose, saccharose, etc. The differences are, however, sufficiently clear to prevent confusion. Proteus vulgaris hardly develops upon slices of artichoke, the color of which it does not modify. Our microbe forms upon this medium

[1] Ogata. Zur Aetiologie der Dysenterie. Centralblatt f. Bakt., 1892, Bd. xi., S. 246.

a yellow mass, while the remainder of the medium assumes a color of intense green. The surface of the nutrient medium rapidly becomes green when agar-agar prepared with artichoke water is employed. The *proteus vulgaris* does not develop in the latter medium. The culture of my microbe upon carrots is white, quite thick; that of the proteus vulgaris is scanty, consisting of very long filaments and rods, intensely stained. (Fig. 39.) When this appearance is compared with that furnished by my bacillus (Fig. 38), the non-identity of the two bacilli becomes manifest beyond all doubt.

Serum reaction furnishes another distinctive character. I employed the serum derived from animals which had received a virulent culture of my bacillus by a branch of the portal vein and which had resisted this inoculation. By putting one drop of this serum in ninety-nine drops of a culture twenty-four hours old, agglutination of the bacillus is obtained in a few minutes. The proteus is not agglutinated, even when a tenfold amount of the serum is employed.

My microbe has been encountered by Dr. Lemoine under similar conditions, viz., in the course of an epidemic among soldiers housed in the École Militaire. He isolated the bacillus in thirteen cases, and found it to be pathogenic for animals. Finally, Dr. Barbier told me he had found, with the assistance of Dr. Tollemer, a bacillus analogous to mine in an epidemic which appeared in the Hôpital des Enfants Malades. These authors practiced inoculations upon rabbits and found intestinal ulcerations in a certain number of them. In one case, in which they inoculated the virus into veins of the ear, they discovered small abscesses in the liver containing the same bacillus.

Influence of Infectious Diseases upon the Liver.

Microbes may reach the liver by various routes. They sometimes spread through contiguity; they thus invade the gland as a result of perihepatitis or even pleurisy. More frequently they follow one of the circulatory systems ramifying in the organ: the portal vein, the hepatic artery, and the lymphatic and biliary vessels. In almost all infections, but more particularly in those which tend to directly involve the intestines, such as typhoid fever, the liver is usually altered. In dysentery the amebæ find their way into its depths in company with other parasites which cooperate powerfully to induce suppuration. The hepatic artery is, in this connection, of less importance; it is through it, however, that septic emboli reach

the liver, especially in cases of ulcerative endocarditis. The possibility of hepatic infection through the lymphatic vessels has not yet been well investigated. Hayem and some other authorities think syphilitic sclerosis of the liver is induced through the lymphatic channels. Microbes may likewise pass from the intestine to the liver by way of the biliary channels; thus are produced angiocholites and, consecutively, biliary lithiasis.

The liver is very often affected in the fetus. During intra-uterine life the individual is in relation with the external world by the umbilical vessels, and it is through them only that pathogenic germs can invade its organism; the microbes must, therefore, pass first to the hepatic gland, which may sometimes arrest them and be subjected to their action. In case infection becomes generalized the liver is the organ most profoundly affected, as is notably the case in syphilis and tuberculosis. What has been stated concerning figurate elements is equally true as regards toxins, which are also capable of producing disturbances and more or less pronounced lesions in the liver. Moreover, this gland must neutralize autogenic toxins produced in excess by diseased tissues and incompletely eliminated by the injured kidneys.

General Characters of the Infected Liver. In spite of its functional disturbances, the liver may appear sound under macroscopic and even microscopic examination. More frequently, however, it presents various alterations. These may be divided into two groups: some are specific, such, for instance, as syphilomata, tubercles, and nodules of glanders. Others are ordinary lesions, and may be encountered in the majority of infections. They are characterized by congestion, degenerations, cellular proliferations, ending at times in the formation of small nodules. The macroscopic appearances of the liver generally depend upon congestion and cellular degenerations.

The infectious liver is, as a rule, enlarged and soft, the latter character being the more pronounced the more rapid the evolution of the disease. Its color varies according as congestion or degeneration dominates. In the former instance the liver is red; such is the case in typhoid fever, in the first days of eruptive fevers, in cholera, and acute intermittent fevers. When degeneration is predominant the liver is pale, yellowish, anemic, at times covered with ecchymoses, which may be more or less extensive.

When the infectious liver is examined at an advanced period, two orders of cellular lesions are found: degenerations of the hepatic cells

and accumulation of round cells. The cells swell, compress the capillaries, and obliterate their lumina; the initial congestion is followed by anemia. The cells are swollen and, at least in the beginning, contain several nuclei and present fine karyokinetic figures. They subsequently undergo hyaline and vitreous degeneration, as is observed particularly in typhoid fever and cholera. In rarer instances the process is characterized by coagulation necrosis, by transformation of the cells into a vitreous mass without any colorable nucleus. This process is localized and of less importance; it is the death of the cells. Reactionary phenomena are coincidently produced which account for proliferation of the nuclei. Fatty degeneration is very rare; it occurs only in diseases of long duration, in chronic suppurations, in which it is explained by diarrhea and cachexia of the patients. The biliary channels at the same time undergo proliferation and newly-formed canaliculi appear, which are especially marked in subacute forms.

The interstitial lesions consist in the formation of infectious nodules (Friedreich, Wagner, Weigert, Hanot, Legry). These are rounded, oval, or triangular in shape, and occupy any point of the lobule, filling about one-twentieth part of it. They are formed of masses of round cells contained in a granular substance; around them the hepatic cells have suffered granulofatty degeneration. The cells constituting them are probably of various origin; leucocytes, cells of the interstitial tissue, probably also altered hepatic cells contribute to form the masses. Finally, instead of being united in the form of nodules, the cells may be distributed so as to form interlobular or intralobular bands—a true embryonal cirrhosis which may subsequently develop into chronic sclerosis—well studied by Hanot and his disciple, Gaston.

Semiology of Infectious Liver. There is no method enabling the physician to determine during life the functional value of the liver. To this end rather crude procedures and indirect means are employed. For instance, the size of the organ is taken as a basis. It is not possible, however, to establish a relationship between atrophy or hypertrophy of the liver and its function. It is better at times to judge the state of this organ by disturbances observed in other parts of the economy. These disturbances are of two orders. Some, probably of reflex origin, are expressed by pulmonary congestion localized at the right base and a *bruit de galop* of the right heart. The others, more important, are of toxic origin. Delirious or coma-

tose, even convulsive, manifestations may occur. The functions of the kidneys, however, are more disturbed than the nervous system. Hepatic inadequacy results in renal inadequacy, as expressed by decreased secretion. At the same time, in consequence of disorders induced by the hepatic disturbances in organic metabolism, urea is diminished, the extractive matters are increased, and abnormal substances, such as albumin, peptones, etc., appear, and what is more peculiar to hepatic disorders, various pigments, normal or modified biliary pigments, and urobilin are present in the urine.

Icterus is quite rare in the course of infections and, when present, is of rather unfavorable prognostic significance. In a large number of cases, however, it is of a simple catarrhal nature, and does not render prognosis any more serious. Some authors believe this catarrhal icterus is due to the fact that the bile is more viscid and is partially retained; others assert that there is polycholia.

In certain instances the symptoms assume the type of those observed in the course of grave icterus. This has occurred in cholera, scarlatina, and typhoid fever; the cellular alterations are so intense that autointoxication by hepatic inadequacy is produced.

Action of Infections upon the Pancreas.

The difficulty of recognizing disorders and lesions of the pancreas during life and its rapid putrefaction after death have greatly hindered its study. In spite of important works, among others those of Carnot[1] and Klippel, we are in possession of no sure symptoms enabling us to determine the part taken by the pancreas in infectious processes.

The pancreas may be affected in the course of general infections, such as measles, variola, pneumonia, septicemias, and pyemias. Pancreatitis may also occur in enterites, typhoid fever, dysentery, and cholera. The anatomico-pathological study, completed by experimental investigations, has revealed a whole series of lesions from diffuse to hemorrhagic and suppurative pancreatitis. These lesions may be repaired. In many instances, however, as in the case of the liver, they become the starting point of scleroses, and may subsequently end in cirrhotic atrophy of the gland. Pancreatic diabetes is probably thus engendered.

[1] Carnot. Recherches expérimentales et cliniques sur les pancréatites. Thèse de Paris, 1898. Richardière and Carnot. Maladies du pancréas. Traité de médecine et de thérapeutique, Paris, 1898, t. v., p. 9.

It is well to remark that sclerosis may occur in the absence of all infection of the gland under the influence of toxins engendered in other parts of the organism. Dr. Carnot has described a tubercular sclerosis of the pancreas which may be compared with similar scleroses developing in other organs and notably thyroidian sclerosis.

Influence of Infections upon the Kidneys.

The study of renal lesions in the course of infectious diseases is comparatively easy, since examination of the urine, especially search for albumin and casts, enables us to appreciate the functional conditions and lesions of the kidneys.

All infections, even when benign and localized, may give rise to renal alterations. Pneumonia and the various pneumococcic infections produce diffuse nephritis remarkable for the frequency of hematuria. Cholera induces renal lesions which seem to play an important rôle in the pathological physiology of this malady, and explain certain symptoms. Syphilis and tuberculosis give rise to acute or chronic processes.

Among infectious diseases scarlatina causes the most interesting renal phenomena. Albuminuria is frequent, appearing at times during the stationary period, and in other cases during convalescence. It was absent in only one of the author's cases ending fatally—such fatal cases constituting 53 out of a total of 2157 scarlatina cases. Scarlatinal nephritis is generally considered to be of little gravity. It is true that even when it gives rise to uremic phenomena, recovery is possible. Besides the 53 cases above mentioned, the author's statistics show 663 other patients in whom scarlatina was complicated by albuminuria, and who recovered. It is important to note. however, that although the acute symptoms subside far more readily in scarlatinal nephritis than in all other varieties, the patient incompletely recovers. Nephritis too often passes into a chronic state either because albuminuria persists or because it reappears on the slightest occasional cause.

The researches of Ponfick, Langerhans, Wissokovitch, Biedl, and Kraus have demonstrated that microbes introduced into the blood are rapidly eliminated by the urine. In certain instances the excretion of bacteria begins at the end of fifteen or twenty minutes. Their passage is often effected without any injury to the kidneys. It is intelligible, however, that, according to the degree of virulence of the germs and the vulnerability of the organ, colonization may

occur, the microbes being there arrested and producing poisons which prove the starting-point of nephritis. In other instances the toxins are brought to the renal glands from other points of the economy. The rôle of the kidneys in the elimination of poisons accounts for the frequency of lesions which these organs suffer in the course of infectious diseases.

Influence of Infections upon the Genital Organs.

Orchitis complicating mumps is never observed in children; it occurs only in adults, following localization in the parotid glands, and at times replacing it as a sort of metastasis. In rare cases orchitis develops coincidently with parotiditis, and in exceptional instances it represents the first and even the only manifestation of the disease. The testicular inflammation lasts four or five days, and never ends in suppuration. Were it not for the danger of tardy atrophy of the testicle, the involvement would be of no gravity whatever. When both testicles are involved prognosis must be reserved from a procreative standpoint.

Typhoid fever has been cited among infections particularly liable to affect the testicles. According to Chantemesse, orchitis occurs in the proportion of 1 to 196 cases; it subsides in ten or twelve days without causing atrophy of the gland. In some cases, however, owing to localization of the typhoid bacillus, suppuration remarkable for its long duration has occurred.

The ovaries are less frequently involved than the testicles; their participation has, however, been noted in typhoid fever, variola, and mumps. Like other parts of the organism, the uterus may be affected in measles, variola, and typhoid fever.

Influence of Infections upon Menstruation. The relations between menstruation and the development of erysipelas have long been noted. We must leave aside those instances in which the coincidence is accidental. For instance, one of our patients had already had six attacks of erysipelas; the seventh attack occurred with menstruation. Genuine menstrual erysipelas always occurs on the occasion of menstruation. These erysipelas attacks are generally so benign as to cause no anxiety, and, therefore, few patients resort to the hospitals. We have observed but 16 such cases out of a total of 1198 erysipelatous women. One of them had had forty-six attacks, always coincident with menstruation.

Erysipelas may at times replace the menstrual flow. A woman twenty-one years of age had had her first erysipelas eleven months before; since that time she had six more attacks, and each time the cutaneous inflammation appeared the catamenial discharge failed to occur. She entered the hospital on March 17th for a quite intense erysipelas replacing menstruation. On April 11th, while she was still in our wards, the menses appeared in a regular manner, and erysipelas did not recur.

In three other cases erysipelas recurred regularly every month before puberty, and, at this period the cutaneous manifestations ceased or persisted. A woman, forty-five years of age, told the author that from the age of seven years to that of eighteen she had every month developed a slight erysipelas; at the age of eighteen menstruation was established and the periodical erysipelatous attacks ceased. She had one attack of erysipelas at the age of thirty-two years, occurring independently of the menses. The menopause occurred at the age of thirty-eight years, and from that time on, while she has had no menstruation, she experienced two attacks of erysipelas, once when forty-one years old, and another for which she resorted to our wards, at the age of forty-five years.

Of all infectious diseases variola is undoubtedly the one which most frequently causes menstrual disturbances. Uterine hemorrhages are observed in 11 or 12 per cent. of the cases which recover. Metrorrhagia generally occurs at the period of invasion; in some cases during convalescence. The action exercised by variola upon the uterus is so marked as to cause bloody discharges even after the woman has reached the menopause. This occurred in a patient forty-five years of age, in whom the menopause had been established six months before. The same happened in a twelve-year-old child who had not yet begun to menstruate. The author has observed the same even in a child five months old.

Menstrual disturbances are particularly frequent in fatal cases of variola. Metrorrhagia complicates 28 per cent. of confluent variola; it is never absent in hemorrhagic variola.

According to our statistics, measles gives rise to premature menstruation in 5 per cent. of the cases and scarlatina in 10 per cent.

Influence of Infections upon Pregnancy and Lactation. It seems to the author that the gravity of infections in pregnant women has been somewhat exaggerated. In this connection erysipelas has been a special subject of study. Clinicians had long since noted the

remarkable relationship existing between erysipelas and puerperal fever. Bacteriological researches have shown that the same microbe is concerned in both instances, and thus have confirmed the data of observation. The facts, however, which the author has collected do not justify the fears of accoucheurs regarding erysipelatous infections.

The author will first consider the influence of erysipelas upon the course of pregnancy. Ancient authors dwelt much upon the frequency of abortions: Wardevell saw 24 abortions out of 25 cases. Recent statistics are far better: Duchein gathered 41 cases, and notes but 14 abortions. Dr. Legendre observed 4 abortions in a total of 13 cases. The author has received 44 pregnant women into his wards. In 25 of these, although several suffered from grave erysipelas, pregnancy continued its course. Nineteen, twelve of whom had reached full term, were confined in our wards; the other confinements took place in the seventh or eighth month.

Erysipelas of the mother does not seem to be dangerous for the child. All those which were born at full term survived and developed well. Only one of them contracted the disease.

Suckling by Infected Women. Shall an infected woman be allowed to suckle? This question is to be answered according as infection is protracted or transitory. In the former instance suckling must be interdicted; such is the rule as regards typhoid fever. In the case of transitory infections suckling may be permitted.

In view of the evil effects of artificial feeding among the poorer classes, the author first permitted erysipelatous women to suckle their children. No harm resulting, he followed the same rule in other infections treated in his wards. The result seemed to be highly gratifying. Out of a total of over 100 children, only two were infected; one of them contracted measles, the other erysipelas from the mother. In both instances, however, the evolution was remarkably benign. The other children presented no disturbance. It is to be remembered that infection diminishes the lacteal secretion and may necessitate mixed feeding for a few days. Only in very grave cases of variola is the secretion so profoundly altered as to render suckling impossible.

The rules are well defined as regards syphilis. It is important that the mother should suckle her child. The laws of Colles and Profeta show that there is not the slightest inconvenience in this practice. If either of them, the mother or the offspring, is alone contaminated, the disease is not transmitted to the other.

As regards tuberculosis, the rule is the reverse of the preceding. Suckling must be forbidden. Not because the milk is very dangerous—Koch's bacillus very seldom passes into the milk—but in the course of this chronic disease the milk is of an inferior quality and, on the other hand, it is wise to diminish the chances of contagion by limiting the contact between the mother and her child.

To sum up, while suckling is to be forbidden in chronic infections, except syphilis, or in prolonged acute infections, it may be permitted in other cases.

CHAPTER XVII.

EVOLUTION OF INFECTIOUS DISEASES.

Incubation. Duration of Incubation in Principal Infections. Invasion. Stationary Period. Course of Local and of General Phenomena. Clinical Forms. Clinical Forms of Pneumonia and of Typhoid Fever. Termination of Infectious Diseases. Defervescence. Crises. Urinary and Urotoxic Crises. Study of Urinary Crises in Pneumonia, Erysipelas, Scarlatina, and Catarrhal Jaundice. Convalescence. Accidents of Convalescence. Relapses and Recurrences. Passage of Acute Infection into a Chronic State. Death. Death by Mechanical Cause. Death by Intoxication. Death by Post-infectious Cachexia.

The evolution of infectious diseases may be divided into four periods or stages: incubation, invasion, stationary period, and decline.

Incubation corresponds to the time elapsing between the deposition of a pathogenic agent in the organism and the first appearance of morbid manifestations. *Invasion,* which indicates the beginning of the disease, may be abrupt or insidious. In the former instance, the moment at which the disease sets in may be noted in a precise manner. Such is the case, for instance, when an apparently healthy individual is suddenly seized with a violent chill. The passage from a sound into a morbid state occurs without transition, and is sharply defined. In other cases the symptoms develop gradually, so that an intermediate period of malaise or indisposition elapses, and it is then very difficult to determine the beginning of the disease. The developed disease remains for a certain time stationary, presenting more or less marked oscillations of aggravation and amelioration; this is the *stationary period.* Then comes the *decline* which, like invasion, may be sudden or progressive. In the former case, a sudden defervescence or *crisis* is said to occur, and the expression *decline* is reserved for the slow course toward recovery.

After the favorable termination of the disease there remains a period, at times of considerable length, during which the functions are re-established progressively, and gradually become normal. This is *convalescence.*

Finally, even when the morbid acts seem to be terminated, the organism may not have completely resumed its former mode of life.

Certain anatomical changes or functional disturbances may persist, remaining inappreciable even on profound examination; but a silent, insidious, morbid evolution continues which terminates at the end of several years in symptoms, disorders, and affections which are not readily traced to their origin.

Such are the various periods observable in the course of infectious diseases. This division is appreciable, especially when evolution follows an acute course. It is far less definite in cases of chronic infection.

Moreover, the morbid evolution may be constantly modified by some unexpected event or complication, or it may be interrupted by death.

Incubation.

Incubation, as above stated, is the time elapsing between the deposition of the morbid germ in the tissue and the appearance of the first local or general symptoms of the disease. This definition, which is applicable only to heteroinfections, must be slightly modified when the process is one of autoinfection. In the latter case the germ is not deposited in the organism from without, and therefore the stage of incubation begins at the moment when the dormant microbe, until then inoffensive, becomes pathogenic under the influence of some excitation. It is intelligible that if the determination of the period of incubation is a matter of difficulty in the former case, it is almost an impossibility in the latter.

During the period of incubation the organism does not always remain passive; it may endeavor to destroy the invading microbes. Should it fail to do this, the disease becomes manifest. It is therefore incorrect to say that an infectious disease is a reaction aroused by the introduction of a microbic agent, since morbid reaction does not necessarily occur in all instances. The microbe may be destroyed or remain quiescent at the point where it was deposited. In order that morbid manifestations may appear, a period of preparation is required which represents a first defeat of the organism. We are thus led to admit the occurrence of three successive stages at the beginning of all infections: introduction or exaltation of the microbe, a latent period of development corresponding to incubation, and a reaction of the organism corresponding to invasion, that is, to the beginning of the disease.

The period of incubation may be silent and unattended by morbid manifestations; then, at a given moment, a reaction is produced,

often quite suddenly. Such, for instance, is the beginning of lobar pneumonia. It is a very curious fact that the microbe should be able to continue secreting its toxins in a progressive manner without giving rise to any disturbance on the part of the organism, and that the organism should act so tardily when it is, as it were, saturated with soluble toxic products.

Even when the beginning is sudden it is often difficult, if not impossible, to determine the period of incubation, since we are not always able to decide as to the moment when contagion occurred. Most frequently patients are unable to give any information. In the eruptive fevers, except variola, it is seldom possible to determine under what conditions contamination has taken place. Even when patients know that they have been in contact with an infected person they do not remember with accuracy the day on which they saw the diseased individual. Others have passed several days at the bedside, and it is evidently impossible to know at what moment contamination was effected. Finally, in cases of prolonged incubation, it may always be asked whether a later contamination which has remained unnoticed has not taken place. Consequently, in order to reach unassailable results, a series of circumstances are required which are seldom realized. The perusal of works on incubation leads to the conviction that an average duration, varying only within narrow limits, exists for the majority of diseases. It would be a grave error, however, to overlook the fact that the period of incubation is at times shortened and at other times prolonged within considerable limits. Nothing in this regard is more demonstrative than the history of venereal diseases, for it is in this class of affections that the moment of contamination may be determined most exactly, and that interpretation is easiest. With syphilis, for example, the chancre generally makes its appearance from twenty to thirty days after infecting intercourse. This average, which is sufficiently wide in its scope, does not, however, include those cases in which the beginning is manifest at the end of ten days, nor those in which it is delayed until the fortieth or even fiftieth day. The variability of this period is proved by the fact that several indurated chancres resulting from a single infection may appear successively in the same individual at intervals of several days. The same variations are observed in gonorrhea. The average is from two to five days, but the discharge sometimes sets in after twenty-four hours or appears very tardily at the end of several weeks. In the latter instance it is assumed that the

microbes deposited in the balanopreputial furrow have not invaded the urethra until a certain time after coitus. With the soft chancre incubation is more fixed and does not exceed twenty-four hours. This figure is confirmed by numerous inoculations practised upon subjects presenting suspicious ulcerations.

Information is quite precise in cases of infection of traumatic origin. In the case of tetanus the period of incubation is from two to three days; in the statistics of the civil war in America we find that in twenty-seven cases the symptoms appeared on the day of traumatism. Bertran (of Elbeuf) has seen tetanus appear five hours after the infection of the wound. It has been stated that incubation at times lasted only two hours. On the other hand, it has in some cases been prolonged thirty and thirty-five days.

In hydrophobia the incubation period is still more variable, the average being thirty days and the minimum fourteen. As to the maximum, a period of eighteen months has been admitted, although there are certain rare instances in which the period of incubation lasted two, three, and even four years. Erysipelas may be considered as occupying a position between traumatic diseases and those apparently spontaneous. Most of the classic treatises fix its period of incubation at three or four days, admitting that it may be reduced to two days or prolonged to twelve. Leaving aside the cases of non-traumatic erysipelas, the beginning of which cannot be determined with accuracy, let us consider the results obtained in cases in which streptococcic infection developed in a wound. In eighty-three cases we obtained accurate information permitting us to fix the time elapsing between the accident and the beginning of the infection. The figures are as follows:

Incubation period from		3 hours	1 observation.
"	"	7 to 18 "	11 observations.
"	"	24 "	14 "
"	"	25 to 48 "	11 "
"	"	49 to 72 "	9 "
"	"	4 to 5 days	8 "
"	"	6 to 8 "	16 "
"	"	9 to 15 "	17 "
"	"	22 "	6 "

In twelve cases incubation was, as we see, extremely short; not the slightest doubt may be entertained as to the evolution, the details of the facts being given. Here is, for example, one of them:

The wife of a physician was preparing to go to a ball. In putting on her ear-rings, which she had not worn for a long time, she pro-

duced a slight abrasion in the ear. This occurred at 9 P.M. On her return home, at 4 A.M., she was taken with a violent chill, fever set in, and her husband noticed in the morning the development of a typical erysipelas. General reaction was, therefore, produced seven hours after traumatism.

When erysipelas develops tardily it may be questioned whether it is truly a case of prolonged incubation, since it is possible that the wound may be infected later and that the streptococcus may not have been introduced at the moment of the accident. We must acknowledge that the problem cannot be solved by clinical observation alone. Experimentation must, therefore, be resorted to. If we inoculate a culture of streptococcus beneath the skin of the ear of a rabbit, erysipelas develops generally within twenty-four or forty-eight hours. At times the incubation lasts three or four days. In two cases the author has seen it prolonged eleven days. Here, therefore, are results of considerable practical consequence. They confirm what is taught by clinical observation and establish that in erysipelas incubation may last only a few hours or exceed a week. But what must we think of the cases in which the period of incubation lasts fifteen or even twenty-two days? All hypotheses are permitted. When, however, the wound does not seem to have been contaminated ulteriorly, we may assume that it was infected as soon as it was produced, whether the microbe proceeded from the soil or from the skin of the patient. Later on some occasional cause, which may often escape notice, favors the development of the dormant germs. The influence of cold or a draught in such cases is thus explained. We had a demonstration of this in several cases in which we saw a recurrence under such influences. Patients who seemed to be completely cured of erysipelas left our wards, suddenly exposed themselves to cold, and in the evening of the following day the infection reappeared and forced them to return to the hospital. In such instances the microbes which still persisted in the skin were exalted owing to transitory weakening of the tissues, occasioned by an auxiliary cause, however common this cause may seem to be.

There is another question. Is there any relation between the duration of the period of incubation and the gravity of erysipelas? Our observations compel us to answer in the negative. In one of the patients who died the incubation period lasted eight days. In two instances erysipelas was grave, followed a wandering course, and was prolonged for three weeks. In one of these cases incubation had

lasted twelve hours, in the other eight days. On the other hand, we have seen a slight erysipelas which lasted only four days and the incubation period of which did not exceed thirty-five hours. In fact, the duration of the period of incubation may be very short in two quite different cases. At times evolution is grave, because the microbe is highly virulent and develops with great rapidity. In other instances, on the contrary, the phenomena appear speedily because the organism is capable of powerful reaction. In this case erysipelas is of a more benign character than if the incubation had lasted longer; the germicidal serum and phagocytes arrive early and more easily overcome the microbes which are already developed. The explanation we propose is not a mere hypothesis; it is supported by experimental data. We have shown, for example, that it is possible to shorten considerably the period of incubation by sectioning the vasomotors distributed to the inoculated ear. Under these conditions the responsive sensitiveness of the operated side is increased and erysipelas develops more rapidly than on the normal side. But its evolution is more prompt and favorable in so far as the lesions, which are often observed in animals in consequence of the streptococcic inoculation, do not appear. Thus, in cases in which the disease is unavoidable it is desirable that it should begin early, since the organism will then combat a smaller number of microbes and will be less profoundly impregnated by toxins.

Among the eruptive fevers, precise information is most easily obtained in smallpox. Its period of incubation is, on an averages twelve days, but it may vary between seven and fifteen. In scarlatina, Sevestre finds an almost invariable average of four to five days, but there are observations recorded in which the period of incubation lasted no longer than twenty-four (Trousseau), twelve (Sevestre), and even seven hours (Thomas). In other cases it has been prolonged to twelve, seventeen, and forty days (Rilliet and Barthez). In two instances reported by Dechambre it lasted seven weeks. It is well to note that these extreme figures are altogether exceptional and that an incubation period of from two to five days answers fairly well to general facts. We have been able to establish the period of incubation in twelve cases. In two of these it did not exceed twenty-four hours. One of the two observations was very precise. It was the case of a man who had seen a friend on his fifth day of scarlatina. On the following day he experienced fever and dysphagia, and the next day the eruption appeared. The incubation period was forty-

eight hours in six cases and three days in another. Finally, three women manifested the first symptoms of scarlatina in sixty-eight, seventy, and seventy-two hours, respectively, after having been admitted as nurses to our scarlatina wards. In surgical and puerperal scarlatinas the incubation period may be very short, and generally does not exceed three days (Paget, Sorensen). This may, perhaps be explained by the fact that surgical or obstetrical traumatism diminishes the resistance of the organism.

The incubation period of measles is from eight to twelve days, with a minimum of four and a maximum of fourteen. That of rubeola is eighteen days, being sometimes prolonged to twenty or twenty-one, and exceptionally falling to eight and even five days (Griffiths). Varicella is said to begin fourteen to fifteen days after contamination. At times it appears after the nineteenth day, but never before the thirteenth. In two personal observations the period of incubation seemed to be seventeen days. According to Steiner, inoculated varicella begins on the sixth day.

Of other infections the incubation period of which has been fairly well determined, we may mention diphtheria, which begins two days after contagion, and at times after seven and even fifteen days (Sanné); and whooping-cough, from two to eight days after. In mumps the incubation period is generally fifteen days. In three cases published by Roth it was exactly eighteen days. In cholera the beginning has at times occurred a few hours after contagion. In other cases it has appeared on the sixth day. In typhus fever an incubation period of twelve days is generally admitted, which may at times be prolonged to twenty-three. The attack has at times occurred almost instantly (Marsh, Netter). In such cases individuals who approach a patient are deeply impressed by a disagreeable odor and are immediately forced to lie down. The following table, which indicates the average, maximum, and minimum incubation periods, is based upon facts recorded by various authorities, upon statistics published by Williams on behalf of a London commission, and upon our own personal observations:

INCUBATION.

	Average.	*Minimum.*	*Maximum.*
Anthrax,	2 days	1 day	3 days.
Bubonic plague,	4 to 6 "	2 days	7 "
Chancre (soft),	1 to 2 "	1 day	3 "
Cholera,	2 to 4 "	1 "	6 "
Diphtheria,	2 "	2 days	15 "
Erysipelas,	4 to 6 "	3 hours	22 "
Influenza,	3 to 4 "	1 day	5 "
Glanders,	3 to 5 "	24 hours	3 months.
Gonorrhea,	3 to 5 "	1 (?) to 2 days	1 to several weeks.
Mumps,	15 "	7 days	30 days.
Malaria,	6 to 10 "	99 hours	Several months.
Recurrent fever,	5 to 6 "	86 "	8 days.
Measles,	9 "	4 days	14 "
Hydrophobia,	20 to 60 "	13 "	18 months to 3 years (?).
Rubeola,	18 "	5 "	21 days.
Scarlatina,	2 to 5 "	7 hours	7 weeks.
Smallpox,	12 "	7 days	15 days.
Syphilis,	20 to 30 "	10 "	50 "
Tetanus,	2 to 3 "	2 hours	35 "
Typhoid fever,	14 "	2 days (?)	21 "
Typhus,	12 "	0 (?)	23 "
Vaccinia,	3 "	2 days	7 "
Varicella,	14 to 15 "	13 "	19 "
Whooping-cough,	8 "	2 "	8 "
Yellow fever,	3 to 4 "	2 "	6 "

To the infections presented in the foregoing list we may add those the microbes of which may remain for a long period of time in a latent state in the organism. Such is the case in tuberculosis and leprosy. The most extraordinary observation is that of Hallopeau: An individual presented the first symptoms of leprosy thirty-two years after having returned from a country where this disease is endemic.

Clinical experience suffices to establish that the duration of the incubation period is very variable, and experimental researches have demonstrated certain causes which precipitate or delay the beginning of a disease. First, there is an idea which should never be lost sight of, that is, the variability in the action of viruses. Viruses may be divided into two groups—*i. e.*, fixed and variable. In this regard nothing is so instructive as the history of hydrophobia. The variable virus is that found in an animal which has accidentally become rabid. The fixed virus is that which has acquired a determined degree of power by virtue of successive passages through animals. By inoculating the virus into animals of the same species placed under the same conditions the phenomena are produced after

the lapse of a perfectly determined period of time. Such is not the case, however, in nature, and the constant variations in virulence result in modifications in the period of incubation. The same result is observed in man. By virtue of its transmission by successive inoculations, vaccinia has become a fixed virus. Its period of incubation is almost invariable. In subjects vaccinated for the first time, the eruption appears seventy-two hours after inoculation, and is well developed in the course of the fourth day. Even with this fixed virus, however, certain variations are observed.

The soft chancre, which is transmitted by direct inoculation just as is an experimental virus, has also acquired a sufficiently fixed power. Hence, the lesion always begins twenty-four or forty-eight hours after contamination. The occurrence of a longer period of incubation must be attributed to inaccurate observation.

It can readily be understood that with viruses of variable potency the greater the energy and number of microbes introduced the shorter will be the incubation period. The period of incubation will also vary with the location of the wound. It will be longer if the affected region is provided with dense cellular tissue and is poorly supplied with vessels and nerves. Such is strikingly the case in hydrophobia. Finally, microbes develop more readily when they are introduced simultaneously with irritating substances or other bacteria, even simple saprophytes, favoring their multiplication.

On the part of the organism all causes of weakening should be taken into account—extensive traumatism, laceration of tissues, modifications of the general condition by overexertion, excesses, alcoholism, intoxications, and previous or present diseases. Lastly, we must not overlook the influence of moral impressions, the power of which is well known with respect to hydrophobia. For example, an individual who has been bitten by a rabid animal no longer thinks of his accident. Suddenly a word reminds him of the bite, and immediately manifestations of the disease appear and rapidly terminate in death. The duration of the period of incubation may also be modified by the responsive aptitudes of the subject. In persons with very sensitive nervous systems the onset will be hastened. In this particular case a short period of incubation constitutes a favorable phenomenon.

Invasion.

Invasion may be sudden, or slow and progressive. In the former instance the stationary period is quickly reached; in the latter it supervenes only at the end of a few days, and is thus preceded by a prodromic period in which the symptoms are inadequate to determine the nature of the morbid process.

As an example of infection with sudden onset, writers always cite pneumonia, and, as an example of slow invasion, typhoid fever. These two illustrations are well chosen. Clinical phenomena are always so variable, however, that a great many exceptions may be mentioned. There are cases of pneumonia beginning in a slow and insidious manner, and there are typhoid fevers characterized by a sudden onset. It is not difficult to understand how progressive invasion is effected. The noxious substances are secreted little by little by the microbes, become diffused in the organism, and influence the cells. When the toxins are elaborated in greater amount their constantly increasing accumulation gives rise to more and more marked disturbances. A sudden onset is more difficult of explanation. Even in pneumonia it is possible that the morbid poison is secreted in a progressive manner, and at first sight the sudden appearance of the phenomena is not understood. The differences are probably due to the mode of action of poisons. This view is, of course, purely hypothetical, but it is supported by some facts. A first result which must be taken into account is that most microbic toxins, unlike poisons properly so called, and notably alkaloids, exert no immediate action. Even when they are introduced into the blood no immediate symptom is produced, but after a period of latency of varying duration the morbid phenomena suddenly appear. This experimental fact has a very important bearing upon our subject. In fact, it may be assumed that in certain cases microbic poisons act clearly and rapidly as they are elaborated. Under such conditions disturbances begin slowly and follow a progressive course. In other instances an oversaturation of the organism will be required in order to produce reaction. This is the first effect of cumulative doses.

Whatever be the mode of invasion, the general phenomena first bear on the nervous system. If invasion is slow and progressive, the disturbances are gradually intensified. These are malaise, headache, dizziness, weakness of the extremities, and incapacity for all

muscular or mental exertion. Delirium, if present, is of the mild, quiet type. Sleep is disturbed only by nightmares or some vagaries. On the whole, the symptoms are not intense, and are established gradually and aggravated in a slow, and often regular, manner. On the other hand, if invasion is sudden the nervous symptoms will be intense and disquieting from the first. The process is of the nature of a true outbreak. There has been a silent accumulation of toxins, and all of a sudden a violent, impetuous, unexpected reaction occurs—*i. e.*, intense chills or, in children, a convulsive attack. At the same time fever develops and rapidly reaches 102.2° or 104° F. (39° or 40° C.).

Headache is intense, and delirium may be excessive from the first. Severe delirious phenomena are mostly, we might say nearly always, observed in diseases characterized by sudden onset and occurring in predisposed individuals. Delirium tremens is altogether exceptional in typhoid fever. It is not so rare in smallpox and erysipelas, but it is especially frequent in pneumonia. It expresses a profound nervous perturbation, and occurs in alcoholic subjects as a result of the toxomicrobic shock, as is sometimes produced by violent traumatism.

In diseases characterized by sudden invasion, a series of symptoms which might be connected with visceral lesions, but which seem to be dependent upon disturbance of innervation, is observed from the very beginning. These are, vomiting without any apparent alteration of the stomach; diminution in the quantity of urine, at times transitory suppression, without the kidneys as yet being affected; intense dyspnea, unexplained by the condition of the lungs, and acceleration of the pulse and arrythmia, which are in nowise dependent upon cardiac lesions. There is a striking discord between the functional and the anatomical conditions.

Thus far we have considered only those cases in which invasion is announced by general phenomena. In other cases, infectious diseases may begin with local manifestations, which at times precede, sometimes accompany, the general reactions, and sometimes they run their course without giving rise to any general phenomena. In certain cases, however, the local lesions develop very rapidly. This occurs in young subjects endowed with a nervous system which reacts quickly and with energy, for example, in children attacked by acute pulmonary congestion. The child is suddenly taken by fever, and auscultation practised immediately reveals an intense

blowing murmur. Everything is again normal on the following day. The fever has subsided, and the murmur is no longer perceptible. These facts, which have been so well studied by Bergeron, Cadet de Gassicourt, and Hirne, must be considered as examples of true abortive pneumonias.

Immediately upon its arrival the microbe gives rise to violent reactions which often result in the instant arrest of its course. The excitation of the nervous system is expressed by a congestive fluxion which arrests the infection. In the same order of ideas, although their meaning is more difficult to understand, we may mention herpes, which is so frequently observed in infections, and urticaria, which appears especially in cases of digestive disturbances. Evidently the phenomena of fluxion are alone capable of making a sudden appearance. The other responsive manifestations develop more slowly, and if they at times appear suddenly it is because their beginning has been effected in a gradual manner and, having already advanced to a certain degree, they suddenly give rise to morbid reactions. There is often a lack of harmony between general and local manifestations. In a certain number of cases the two orders of symptoms begin simultaneously. In others the disease is at first characterized by one or the other series of symptoms. In still other instances local reactions are progressive, while general manifestations are abrupt, and *vice versa*. There exist, therefore, a whole series of different modes of reaction of which clinical experience furnishes well-known examples.

The same infection may sometimes start with local manifestations, and at other times by general symptoms. Surgeons have emphasized this fact in describing phlegmons. They have remarked that the beginning with general reactions indicates a greater virulence of the morbid germ, and consequently a grave prognosis. This remark is correct, but must not be generalized. In erysipelas, for instance, these two modes of invasion occur without one being more benign or more serious than the other.

The duration of the invasion period varies considerably according to the infection under consideration, and is not absolutely fixed in each disease. Authorities have endeavored, however, to establish averages. It is generally admitted that invasion lasts two days in scarlatina, three days in measles, and from two to five days in variola. In the latter infection short invasions are observed, especially in grave cases; long invasions in benign forms. In

erysipelas, invasion is supposed to last from a few hours to a day, and the maximum is fixed at two days.

These rules are fairly exact, but they suffer a certain number of exceptions. According to our personal observations the classical figure is observed in a little more than one-third of the cases of measles in adults. In children below two years of age the period of invasion is generally very short. In scarlatina invasion lasts forty-eight hours in half of the cases; it is not infrequently shorter, but seldom longer. As to variola, the law of Sydenham, accepted by Trousseau, is well known. An invasion of two days or two days and a half indicates a confluent variola; an invasion of three days and a half or four days and more particularly when it lasts five days, indicates a discrete variola. Prof. Jaccoud has modified the formula. He maintains that a short invasion may be followed by a discrete variola, but a prolonged invasion never precedes a confluent variola. Our statistics show that there are exceptions to all these rules, and that variolas have at times been confluent after periods of invasion lasting four, five, and even six days. Moreover, we have inquired as to the applicability of Sydenham's law as modified by Jaccoud to the majority of cases, and we have reached the conclusion that in all forms of variola, excluding the primarily confluent variety, invasion generally lasts three days. In one-third of the cases it does not exceed one or two days. The law of Sydenham-Jaccoud is, therefore, exact in 54 per cent. of the cases.

Stationary Period.

Since the time of Hippocrates it has been customary to admit three periods or stages in the evolution of acute diseases: an invading period, a stationary period, and a period of decline. Jaumes has proposed another division. He admits but two periods—*i. e.*, one characterized by a morbid effort corresponding to the period in which the organism is overwhelmed, and one occurring only in favorable cases, a period of improvement and restoration. In other words, the first period corresponds to the attack of the pathogenic cause, and the second to the curative effort of the organism. This division is quite in harmony with the present-day conception of disease. It would have been perfect if reaction really followed action, and if disease followed a regularly descending course after arriving at its height through a progressive aggravation. In reality the facts are more complex. As we have repeatedly stated, the

defensive reactions begin at the same time as the offensive actions, and at times even before all appreciable symptoms. Consequently, the two classes of symptoms constantly intermingle, with the exception, however, that the pathogenic agent has the advantage in the beginning. The reactions of the invasion period indicate that the organism is defeated, or at least on the defensive. Then comes a period when the struggle assumes a serious character, and the two participants fully display their forces. This is the stationary period, which at times seems to remain unchanged, and at others a series of deviations occurs depending upon the various vicissitudes of the struggle. This period is the most important from a nosological standpoint, since the characteristic symptoms of the disease are fully developed. They are so grouped as to constitute a special type which is easily defined and classified. It is at this moment that a previously hesitating diagnosis may be made more certain.

In studying the stationary period the local symptoms and general phenomena must likewise be taken into consideration. When the local manifestations occupy the external parts they may readily be studied. Such is the case with erysipelas, abscesses, and phlegmons, cutaneous ulcerations and gangrenes.

These are also quite easily recognized when they occupy a mucous membrane which is accessible to exploration, such as that of the mouth and pharynx. In case a deeply seated organ is attacked, the study becomes more difficult; yet, according to the modifications manifested in the functions of the organ and the changes which may be perceived by means of physical examination, palpation, percussion, and auscultation, we can quite exactly determine and follow the evolution of the phenomena produced in the deeper parts of the economy.

In certain cases, even the minutest exploration fails to reveal any organic alteration, because the symptoms are of a general character. The latter consist in responsive manifestations referable chiefly to the nervous system, the secretions, and thermogenesis. The nervous symptoms are those which have already been noted in treating of the invasion period—*i. e.*, headache, incapacity for work, a diminution of psychical acuity, delirium, and, exceptionally, convulsions. The secretions are for the most part diminished. The urine is scanty, the saliva is not abundant, and the tongue is dry. Finally, thermogenesis is also perverted, and there is usually a rise of both peripheral and central temperature.

A comparison of local and general symptoms leads to the following conclusions: Sometimes the local and general phenomena follow a parallel course. They are aggravated or improved simultaneously. They decline and disappear almost at the same time. Sometimes there is a decided discord between the two orders of phenomena. Thus, for instance, the local lesion may subside while the general phenomena grow worse. In such cases there is generally some fresh complication. More frequently the reverse is the case. The general manifestations vanish, whereas the local symptoms seem to remain stationary. This fact is particularly striking in pneumonia. From day to day a sudden defervescence takes place. The temperature, which had risen to 104° F. (40° C.), falls to 98.5° F. (37° C.). The secretions are re-established; the patient experiences a feeling of well-being which makes him realize that his sickness is over, and yet no improvement has taken place in the condition of the lung. On the contrary, the stethoscopic signs are the same as the day before. The same lack of parallelism is observed in erysipelas, but less constantly. The general phenomena subside, while the cutaneous lesion persists without any change. Finally, in certain cases the discord is no longer real, as in the preceding examples, but only apparent. The local lesion seems to remain unchanged, and yet the general phenomena are modified or even aggravated. These indicate either a local change, which we are thus enabled to recognize and predict, or a new perturbation, perhaps a commencing complication.

In order to recognize the nature, follow the evolution, establish the prognosis, and predict the possible accidents of a disease, we must at the same time take into account the local and general manifestations and their harmony or discordance.

Let us first consider the *local phenomena.* Five events are possible·

1. The local lesion, which began during the period of invasion, is not modified during the stationary period, but follows a very simple evolution, increases gradually, reaches its height, and then, in favorable cases, resolves. No notable change in its character or aspect appears. Of numerous illustrations it will suffice to mention mumps, erysipelas, and gonorrhea. We might add scarlet fever and measles, in which the eruption characterizing the stationary period extends progressively to all parts of the skin, but always preserves an invariable aspect.

2. In other cases the local lesion is modified from day to day. An abscess may be taken as an example in which exploration is easy. At first induration is present, then the lesion undergoes softening, becomes fluctuating, and opens exteriorly. A like course may be observed in cases of visceropathies. In simple bronchitis there is a period of crudity, when expectoration is difficult and painful. Then a period of coction, when the sputa become mucopurulent and are easily expectorated. Examination of the sputa as well as auscultation demonstrate the changes characterizing these two periods. By the same methods of exploration we can follow perfectly the evolution of a pneumonic focus: In the beginning there is pulmonary obstruction resulting from the exudations, and auscultation reveals crepitant râles. Next, a fibrinous exudation into the air cells takes place; this is the period of red hepatization, characterized by tubular breathing. Lastly, the exudation softens and auscultation reveals râles of resolution.

3. Instead of remaining localized in a region the local lesion extends and invades the neighboring parts. Here erysipelas and pneumonia may again serve as examples. While often circumscribed, erysipelatous inflammation sometimes extends over a great part of the skin. At times it covers the entire surface of the body. This is a particular clinical form justly described under the name ambulatory erysipelas. The same evolution may be observed in the lungs, under which circumstances pneumonia is designated as migrating. In certain, but fortunately very rare, instances a local lesion grows both deeper and larger, causing considerable loss of substance. This is known as *phagedenism,* and is observed chiefly in the soft chancre, which lesion may destroy the penis, invade the scrotum and thighs, and follow a serpiginous, extensive course, the duration of which may be months or even years.

4. The local lesion sometimes progresses by successive stages. When the lesion seems on the point of subsiding, or has even disappeared, a recidive sometimes occurs in the region primarily attacked. This is observed especially in erysipelas. In other instances the recurrence takes place in parts more or less distant from the region primarily diseased, for example, orchitis, occurring in mumps, and endocarditis, pericarditis, or meningitis in pneumonia. The pathogenic agent thus tends to colonize distant tissues or organs. The process is, as it were, a relapse at a distance. In a certain number of cases the appearance of a new morbid focus coincides with the

disappearance of the primary focus. This is *metastasis*, the best illustration of which is furnished by the history of rheumatism: when cerebral manifestations appear the swelling in the articulations subsides, the pain disappears, sometimes with astonishing rapidity; a transfer of the fluxion from the articulations to the nervous centres occurs.

5. The local lesion may be modified by an additional infection. Pathogenic microbes implanting themselves, for example, in a part already diseased, give rise to suppuration, and may even invade the economy. In gonorrhea the gonococcus often remains localized in the urethra. Common bacteria, however, soon join it, and may subsequently induce very serious disturbances. Although the gonococcus may at times invade the organism, the so-called gonorrheal rheumatism generally depends upon ordinary pyogenic bacteria. The process is one of attenuated purulent infection to which the agent of gonorrhea has merely opened the way.

General phenomena usually follow a course parallel to that of local symptoms. During the stationary period they may remain quite unmodified. In pneumonia, for instance, the fever remains about 104° F. (40° C.). Dyspnea, thirst, and headache remain about the same during the entire evolution. The same remark holds true of typhoid fever, although some differences are revealed by a more careful study.

In some instances the general symptoms are modified several times, so that the stationary period has been divided into a certain number of secondary periods. In other cases the general phenomena keep pace with the local, as is observed in smallpox. Sometimes the changes do not seem to harmonize. Thus, in tubercular meningitis three periods, which apparently do not correspond to anatomical changes, have been described according to the general symptoms. After a phase characterized by violent headache, fever, constipation, and vomiting, a marked remission occurs, which lasts nearly a week. The patient is believed to be convalescent, when the symptoms reappear and go from bad to worse, ending in death.

In a certain number of infections the modifications in the general phenomena express the generalization of a primarily local microbic process. Such is the case with malignant pustule. The lesion is at first characterized simply by a cutaneous eschar. In certain cases phenomena of general infection are subsequently produced, indicating the invasion of the economy by the pathogenic agent. Likewise,

in cases of septicemia or pyemia consecutive to local lesions, the changes occurring in the general symptoms reveal the invasion of the organism.

Nosologists have divided the stationary period of diseases by taking into account both the modifications occurring in the local symptoms and the general manifestations. Undoubtedly these divisions are not always perfect. Didactic descriptions are necessarily schematic and cannot give an exact idea of the complexity of clinical phenomena. We have above referred to tubercular meningitis. Its evolution in three phases, admitted by all classical treatises, is, however, of rare occurrence. The phenomena very seldom, if ever, progress with such quasi-mathematical precision as has been attributed to them. The clinical types are, in reality, far more complex and variable than may be supposed from classical descriptions.

The general phenomena have been divided into continued, remittent, intermittent, and irregular, mainly upon the basis of the precise data of medical thermometry. After the details which we have given in treating of the febrile process (p. 355), it will suffice to say that general morbid manifestations run a course nearly parallel to that of fever, increasing or diminishing with it, and thus presenting the same daily variations. There are, however, exceptions to this rule. There may be dissociation between the two orders of phenomena. Febrile manifestations may diminish while the other symptoms become aggravated. Such, for instance, is the case in hepatic or renal lesions. We have then to deal with particular clinical forms.

Clinical Forms. The stationary period of infectious diseases being the longest and especially the best characterized, has served to differentiate clinical types. On the basis of their evolution cyclic diseases may be admitted in which the duration is sufficiently defined and determined by a regular succession of morbid phenomena. Pneumonia, typhoid fever, and eruptive fevers belong to this category. It should be remembered, however, that the figures given by authorities are subject to numerous variations. The term of nine days assigned to pneumonia, and of three weeks to typhoid fever, represent averages which are seldom realized. Nevertheless, the term may be retained in contradistinction to non-cyclic diseases, such as diphtheria and erysipelas, whose capricious course defies all efforts at averaging. Even in those diseases in which the stationary

period is best determined very great variations may be observed. In certain cases the evolution is shortened, either because the disease assumes a very acute, speedy course, causing death very rapidly, or, on the contrary, because it follows an abortive course. Pneumonia is again a good illustration. This infection may kill at times within a few hours, as occurs in the aged, in diabetics, and in individuals suffering from previous diseases, notably erysipelas. In this connection we may also mention the speedy types of scarlatina, smallpox, and cholera. Death may supervene at the beginning of the stationary period, and even before the latter is clearly established.

Pneumonia likewise furnishes the best illustration of an *abortive infection*. The disease begins suddenly, reaches the stationary period, and all at once defervescence occurs on the third or fourth day. Abortive typhoid fevers have also been described, and we may likewise admit the occurrence of abortive eruptive fevers—*i. e.*, such as are cut short after a prodromic period. Thus, an individual who has been exposed to the contagion of variola is seized with all the premonitory symptoms of this disease; then the symptoms disappear and the eruption is characterized by two small pustules. This is evidently an instance of an attack of variola deserving the name abortive. Notwithstanding the intensity of the symptoms of invasion, the disease is cut short. Cases of abortive erysipelas, which stop suddenly after the period of invasion, at the very beginning of the stationary period, may also be admitted. It is useless to multiply examples. While these facts are already well known, the author believes them to be far more frequent than is usually supposed. Many febrile paroxysms, transitory indispositions, and sudden chills, which are followed by no special manifestations whatever and which run their course in a day and sometimes in a few hours, are to be accounted for by an infection that is abortive. Consecutive to infections occurring during convalescence from eruptive fevers or erysipelas, we often see febrile paroxysms which, apparently, are referable to no other cause. This is demonstrated by the fact that numerous transitions are observed between the ephemeral fevers, which can in nowise be accounted for, and those which indicate relapse or a complication.

By the side of diseases aborting spontaneously should be placed those aborting in consequence of therapeutic intervention. Cases of this kind, formerly rare, will become more and more frequent as we become better acquainted with specific medication. The latter

is sometimes represented by vegetable or mineral products. Such are the salts of quinine, which arrest malarial infection, and the salts of silver, which stop a beginning gonorrhea, and especially the preparations of mercury, which suspend the evolution of syphilis. At present specific and abortive remedies are looked for in substances derived from immunized animals. The results obtained by serum therapy inspire us with the hope that the time is not far distant when it will be possible to arrest the evolution of a great number of infectious diseases.

The acute infections, even when they generally follow a cyclic course and terminate within a well determined time, may in some cases be prolonged beyond the usual limits. For instance, pneumonia, instead of lasting nine days, may not reach defervescence until toward the twelfth or even the fifteenth day. Likewise, typhoid and eruptive fevers are not infrequently prolonged in an unusual manner, although examination of the patient fails to explain the persistence of the morbid symptoms. There is, so to say, a torpidity of the organism which fails to produce the special conditions capable of arresting the infection.

In a great number of cases, however, prolongation of the disease is due to a particular course or to the influence of complications. The evolution is prolonged as the result of *successive invasions.* At the moment when the infection is believed to have nearly terminated a new focus is produced. Pneumonia and typhoid fever may evolve in this manner, and, although the new attack is generally of shorter duration than the first, the total duration is thereby considerably prolonged. This mode of evolution, while rare in the diseases above referred to, is the rule in certain infections. Such is the case with recurrent typhus, intermittent fever, and varicella, the duration of the last-named disease being extremely variable on account of the variation presented by the course of successive recurrences. In certain cases the recidive of morbid symptoms is preceded by a certain interval of recovery. A recurrence is then said to have taken place. As in the case of relapse, recurrence is generally less grave than the first attack; but this rule is subject to a great number of exceptions.

Finally, morbid evolution may be prolonged by reason of complications occurring during the stationary period or convalescence. New phenomena, mostly referable to superadded infections, may thus lengthen the duration of a disease for a considerable period of time.

It is evident that nothing but hypotheses can be advanced as to the causes which intervene to abridge or prolong infections. Aside from those cases in which secondary complications are responsible, it is not understood why morbid action is cut short and then reappears when defervescence is about to set in or even after convalescence has began. The solution of these problems is intimately connected with the study of predisposition, immunity, and the mechanism of recovery. If, as is generally admitted, recovery is effected by virtue of chemical and dynamic modifications produced within the organism; if it is dependent upon an increase of the germicidal power of the tissue fluids and upon the phagocytic activity of the cells, the duration of the disease will, of course, depend upon the rapidity of the organic changes, namely, upon the responsive potency of the economy. Relapses, on the other hand, would be due to an insufficiency of reaction. This explanation, however, is inadequate. What we desire to determine are the causes or conditions which arouse the responsive activity of the economy promptly in one case, slowly in another, and incompletely in a third. The question is thus reduced to a problem of a much more general nature. In a very great number of conditions morbid reactions are observed which are partly dependent upon the nervous system and partly upon the state of general nutrition. These reactions vary considerably from one subject to another, and this variability is connected with the hereditary or personal antecedents, special innate characteristics, and idiosyncrasies of the individual; in brief, with the various causes to which we have constantly referred to explain the development and course of diseases.

Differences in reaction likewise explain differences in termination. When reaction is energetic and timely it succeeds in destroying the invading microbes. If slight and slow it only arrests their progress, and the process passes into a chronic condition. If too weak or too tardy it fails to save the organism, and the disease terminates in death.

These considerations suffice to demonstrate that the same infectious disease may present varied symptoms and follow an extremely variable evolution. Supposing all conditions to be the same as far as the microbe is concerned, the influence of the organism makes itself constantly felt and contributes to modify the scene. Therefore, a certain number of clinical forms have been admitted. These divisions are evidently arbitrary. In order to establish them,

the various cases encountered have been compared with an habitual average type, running its course without the intervention of any unusual influence. In this way clinical forms have been grouped under two heads: First, according as modifications depend upon some anomaly in the course, morbid symptoms, or localization. Second, according as they are due to the condition of the subject. With some variation this division may be applied to all infections.

In order to fix the ideas, let us consider the two diseases in which clinical types are the most numerous and the most varied, namely, pneumonia and typhoid fever.

The following two tables will show how clinical forms may be classified. The terms sanctioned by usage are sufficiently clear to make description unnecessary:

CLINICAL FORMS OF PNEUMONIA.

I. Divisions Based on the Study of the Disease.

1. *According to the course.*
   - Abortive pneumonia.
   - Speedily fatal pneumonia.
   - Prolonged pneumonia.
     - Double.
     - With successive foci.
     - Migrating.
   - Infecting pneumonia.

2. *According to the morbid elements or symptoms.*
   - Inflammatory pneumonia.
   - Adynamic pneumonia.
   - Ataxic pneumonia.
   - Pneumonia with icterus.
   - Bilious pneumonia.

3. *According to localization.*
   - Pneumonia of the base.
   - Pneumonia of the apex.
   - Central pneumonia.
   - Massive pneumonia.
   - Pleuropneumonia.

II. Division Based on the Condition of the Subject.

1. *According to age.*
   - Pneumonia of children.
   - Pneumonia of the aged.

2. *According to the previous state of health.*
   - Pneumonia of cachectics.
   - Pneumonia of drinkers.
   - Pneumonia of the obese.
   - Pneumonia of diabetics.
   - Pneumonia of bronchitics.
   - Pneumonia of the tubercular.
   - Pneumonia of those suffering with malaria, etc.

3. *According to the coexistence of another infection.*
Pneumonia of typhoid fever.
Pneumonia of erysipelas.
Pneumonia of acute articular rheumatism, etc.
Pneumonia of influenza.

CLINICAL FORMS OF TYPHOID FEVER.

I. Divisions Based on the Study of the Disease.

1. *According to the course.*
Abortive typhoid fever.
Prolonged typhoid fever.
Speedily fatal typhoid fever.
Typhoid fever with relapses.

2. *According to the morbid elements.*
Mucous typhoid fever.
Ambulatory typhoid fever.
Inflammatory typhoid fever.
Bilious typhoid fever.
Hemorrhagic typhoid fever.
Ataxic typhoid fever.
Adynamic typhoid fever.
Putrid typhoid fever.
Hyperpyretic typhoid fever.
Sudoral typhoid fever.

3. *According to the localizations.*
Nervous forms.
Meningeal.
Spinal.
Thoracic form.
Gastric form.
Icteric form.
Renal form.
Cardiac form.
Septicemic form.

II. Divisions Based upon the Condition of the Subject.

1. *According to the age.*
Typhoid fever of children.
Typhoid fever of the aged.

2. *According to the previous condition of health.*
Typhoid fever of cachectics.
Typhoid fever of the obese.
Typhoid fever of drinkers.
Typhoid fever of the tubercular.

3. *According to the coexistence of another infection.*
Typhoid malaria.
Laryngotyphus.
Pneumotyphus.

Termination of Infectious Diseases.

We have repeatedly shown that the organism is provided with means of protection which prevent penetration and multiplication

of pathogenic germs. The latter may succeed in invading the economy only when the vigilance of the cells is diverted for a moment and the fluids are altered by some affection. The disease then manifests itself. Modifications in cellular nutrition are immediately produced, however, which transform the blood, the fluids, and the tissues, and make of them unfavorable culture media for the pathogenic agent. Two events are then possible: 1. In some cases the changes are produced slowly and progressively; the organism gradually rids itself of the germs and neutralizes the action of the toxins which impregnate it. Defervescence is slowly effected; the fever is progressively reduced by *lysis*, and the various functions consume a more or less long period of time in returning to their normal condition. It is, therefore, possible to follow the progress of recovery day after day. This is what takes place in typhoid fever. 2. In other instances, on the contrary, the termination is abrupt and sudden as in pneumonia. It is then said that a *crisis* has occurred.

Crises. From the earliest antiquity it has been noted that certain diseases may present sudden changes in their evolution. This is *crisis*, which supervenes when the corrupt humor (*humeur peccant*) has undergone coction. Nature expels it from the body or causes its deposition in some part of the economy. The latter result was formerly considered fortunate or unfortunate according as deposition occurred in an organ of little importance or indispensable to life: These ideas led Hippocrates to formulate the following definition: "A crisis in diseases is either an exacerbation, decline, a metaptosis, another affection, or the end."

The crisis, however, did not occur at undetermined periods. It was produced on fixed days, called *critical days*, which corresponded to weeks or half weeks—that is to say, to the fourth, seventh, tenth, fourteenth, seventeenth, and twentieth days. The critical days were preceded by the *indicating* days, when an exacerbation of the symptoms was usually observed. We must add that Hippocrates did not regard the critical days as possessing an absolute value. The crisis might occur twenty-four hours sooner or later. Galen, on the other hand, attributed to each day an absolute significance. He contended that acute diseases did not last more than forty days, and considered the crisis as a sudden reversion to health.

The latter definition has prevailed. At the present day the name *crisis* is reserved for cases in which the change is favorable. In infectious diseases this change is characterized by the following

phenomena: A sudden fall in temperature, a rapid increase of the urine, the re-establishment of secretions, and the elimination of noxious substances accumulated during the disease. According to prevailing ideas or the conceptions of the observer, attempts have been made to define crisis by thermal defervescence or by urinary modifications. In recent years, attention having been drawn especially to the modifications of cellular activity, Dr. Chauffard has proposed the following definition: An intimate and sudden act which terminates the morbid evolution and at the same time gives rise to an ensemble of nutritive and functional mutations.

As we are dealing only with infections, we may look for the characteristic nature of the crisis in the most striking clinical phenomena which occur at this moment of evolution. The symptomatic modification is so marked as to have sufficed to reveal the existence of crises before the introduction of the modern methods of investigation, such as thermometry, urology, and the investigations on nutrition.

An individual who was deeply infected on the previous evening is found completely cured on the following morning. This is the clinical characteristic of the crisis. Setting aside all theoretical discussions, we may adopt the following definition: "Crisis is characterized by the sudden disappearance of morbid manifestations." We do not say morbid phenomena, since the local lesion persists; it is the general reactions that subside. As we have repeatedly stated, these reactions are dependent upon intoxication. Consequently cessation of the disturbances indicates that the poisons have been abruptly eliminated or neutralized. The study which we are about to undertake will show that the latter hypothesis is the more probable. On the ground of the results acquired by the study of artificial immunity it may be admitted that neutralization of the poisons depends upon a modification in the cellular nutrition which protects the anatomical elements against the toxic influence. If this is true we may place by the side of the symptomatic definition above proposed a definition drawn from the very essence of crisis—*i. e.*, from the study of pathological physiology. Therefore we may say: "*Crisis is essentially characterized by a sudden neutralization of microbic toxins, namely, by an immunity conferred upon the cells against their action.*" To those who may wonder why this terminal modification is produced or rather manifested in a sudden manner we shall answer that the situation is precisely the same at the period

of invasion. For instance, pneumonia begins and terminates with the same instantaneousness.

Supersaturation of the organism by the toxins was necessary in order for a reaction to be produced and for the disease to be established. Likewise, supersaturation of the organism by antitoxins is necessary in order for the disturbances of toxic origin to be neutralized.

There is an interesting fact that had not escaped the attention of ancient observers, namely, that crisis is often preceded by the so-called precritical phenomena, consisting in, an at times, alarming aggravation of the symptoms. The temperature rises to a higher figure than on the preceding days. The pulse is weaker and more rapid. Dyspnea is very intense, and sometimes the body is covered with cold perspiration. The subjective sensations experienced by the patient are in harmony with these objective disturbances, and hence increase the anxiety of those about him. The contrast is still more striking when the individual seems to be cured the next morning.

In other cases the crisis is preceded by a procrisis. The temperature is suddenly reduced, and may even fall to the normal. The other symptoms subside, and one might believe the evolution at an end. In the evening, however, the disturbances are renewed, to be terminated in a definite manner on the following day. In still other cases a false crisis occurs. During twenty-four or forty-eight hours a relative subsidence takes place, and the temperature is lower than on the preceding days. Then the morbid symptoms are again renewed to disappear suddenly and definitively a few days later.

In most cases the crisis is produced during the night. It is, therefore, surprising to see the patient who was very sick the previous evening completely cured in the morning. The general phenomena have disappeared. The patient realizes this by the feeling of well-being which, doubtless, constitutes one of the most astonishing manifestations. He has the feeling that the disease is at an end and that he has entered upon convalescence. The tongue, which was dry, becomes moist. The skin, which was dry or covered with cold perspiration, recovers its agreeable moisture. The pulse, which was weak and rapid, becomes strong and slow. The change which is at present most easily observed is the sudden fall of temperature. The patient who on the previous day had 104° or 105.8° F. (40° or 41° C.) has no more than 98.6° F. (37° C.). This reduction of several

degrees is produced within twelve hours. In some cases, however, it is effected more slowly—in thirty-six hours. At times the thermometer shows a fall to a subnormal degree, not exceeding 96.8° F. (36° C.), and the temperature may remain at this point for several days.

The sudden and profound change produced at the moment of crisis may give rise to new nervous reactions which constitute the so-called epicrisis. In children this is manifested by convulsions; in the aged by collapse, which is sometimes so marked as to make it a difficult matter to warm the patient. In adults, delirium and in some instances *delirium tremens* occur. I have observed several cases in which patients, who had manifested not the slightest intellectual disorder during the stationary period, develop delirium, sometimes of an intense character, at the moment of recovery, strangely contrasting with the amelioration or disappearance of the other symptoms. The intellectual disturbance, however, is rapidly cured, and does not indicate an unfavorable prognosis. Its pathogenesis is the same as that of the initial delirium. The change suddenly occurring in the economy has disturbed the equilibrium or the quietude of the predisposed nervous system, thus provoking violent reactions.

Special attention must be devoted to changes presented by the blood and the secretions. Dr. Hayem has described a *hemic crisis*, in which the white corpuscles, increased in number during the disease, resume their normal number. The red corpuscles progressively diminish, and at the time of the crisis an activity on the part of the hematoblasts occurs, designed to increase the red globules. We have already referred to the moisture of the skin. At times this cutaneous manifestation is more intense. Sweating is profuse, and serves probably for elimination of the toxins. There may also be observed other manifestations, such as erythemata, outbreaks of urticaria and herpes, sometimes diarrhea, a bilious attack, or epistaxis.

During the disease the quantity of urine progressively diminishes. At the moment of the crisis a discharge occurs. The polyuria is very abundant. Voiding of two and three litres is not rare. The urine is less highly colored than during the stationary period. At this time it corresponds to the numbers 4 and 5 of the scale of Neubauer and Vogel. At the time of defervescence it corresponds to the numbers 2 and 3. Not infrequently the density is increased. In one instance

I found it to be from 1.025 to 1.031. The reaction is often neutral and sometimes alkaline. The soluble substances undergo still more interesting variations. The urea, which may have been reduced to 12 or 15 grams during the stationary period, rises to 30 or 40 grams. The chlorides, which were represented by 1 or even 0.8 gram, reach 10 and 12 grams. The modifications in the amount of chlorides have been attributed to the diet. This opinion is inadmissible, for it is contradicted by the abundant discharge at the moment of recovery. It is also known that if chlorides or iodides are administered to pneumonia patients, these substances accumulate in the organism and are eliminated only at the time of crisis. Likewise, the phosphates and the sulphates increase when defervescence is established, although in less notable proportions.

The same is true with regard to those poisons which are normally excreted by the urine, they being in great part retained in the organism during the disease. During the stationary period the toxicity of the urine progressively diminishes. At the time of crisis it is considerably increased and reaches or even exceeds the normal figure. It should not, however, be concluded from this result that recovery is due to the sudden elimination or to the urotoxic discharge. On the contrary, the reverse is true. Crisis appears because the patient has recovered. This is proved by the fact that in certain cases the urinary crisis occurs twenty-four hours before, or, what is more demonstrative, after recovery. Thus, the patient being cured, he is capable of rejecting the poisons which impregnate his organism, but to which he had already become insensible.

Crisis in Pneumonia. The disease in which crisis is best characterized is incontestably lobar pneumonia. In typical forms the temperature falls to the normal within a night.

Pneumonia does not always terminate in this manner, however. This infection is, perhaps, the one in which the symptoms and evolution are most modified within the last years. Thus, we quite often see the termination effected in a slow and progressive manner. The fever is reduced little by little, then it persists for days and even weeks. Under such conditions diagnosis becomes difficult and wavers between a pneumonia with a slow course and a pulmonary tuberculosis. Even in such cases, however, certain critical manifestations are found, especially some interesting modifications in the characters of the urine.

Let us first consider the observations in which the crisis is quite

clear. In such cases the quantity of the urine is increased, but this phenomenon does not always coincide with defervescence. It may begin a day or two earlier or, on the contrary, appear only at a later period. At times the polyuria is not established until the moment of convalescence. The amount of urea is sometimes increased, at other times diminished, while the *chlorides are always increased.* Furthermore, we have pursued, with Dr. Gaume, some researches on the variations of the urinary toxicity, studying from the standpoint of the urinary syndrome eleven patients suffering from pneumonia. In seven of the cases the termination was effected by sudden defervescence. In two others the fever terminated slowly after having presented numerous variations. In the last two cases the disease ended fatally.[1]

In the first seven cases polyuria was present only twice. The increase of the urea, however, was very marked. From 13 grams, which was the figure obtained during the stationary period, the amount of urea rose suddenly to 35 and 40 grams and even 50 grams. This excess was observed on the day of the crisis and the day following. The modifications in the chlorides were still more striking. During the stationary period we found 0.8 to 2 grams. On the day following defervescence the figure rose to 10 and 12 grams. During the disease there was a notable diminution in the urinary toxicity, it being two or three times less than under normal conditions. This result may be partly attributed to the fact that the patient was confined to a milk diet; but this condition is not sufficient, for it cannot explain the increase of toxicity at the moment of the crisis, when the diet was exactly the same as before. I believe, therefore, that the various urinary poisons, like the chlorides, are retained in the organism and are eliminated at the moment of the defervescence. A urotoxic discharge is thus produced, lasting for a day or two.

Thus, urinary toxicity is very low during the febrile period of pneumonia, and it often diminishes as the disease advances; then a urotoxic discharge suddenly supervenes, lasting from twenty-four to forty-eight hours, and reaching its maximum on the day of thermal crisis, exceptionally on the following day. After the crisis this toxicity slowly diminishes in some cases, rapidly in others, and may again fall to extremely low figures during convalescence.

[1] Roger and Gaume. Toxicité de l'urine dans la pneumonie. Revue de médecine, April 10, 1889.

In two of our cases the fever, instead of terminating in a sudden manner, was reduced slowly. In one of them the urotoxic crisis was produced at the moment when the temperature had begun to decline, and lasted two days, presenting the usual characters. In the other case an incomplete crisis was first observed, coinciding with a urotoxic crisis. Subsequently the fever recurred and the urinary toxicity again diminished. A new urotoxic discharge, a little less pronounced than the first, occurred three days later. From this moment on the course of the disease tended rapidly toward recovery.

Finally, in two of the cases the disease terminated in death, but the evolution was in several respects comparable to the preceding two cases. The course was prolonged. There was no defervescence, but several febrile subsidences occurred, coinciding with urotoxic discharges.

All these facts concur to demonstrate the existence of a urotoxic crisis, even in fatal cases, although in the latter the discharge of the poisons is not well marked.

It would evidently be very interesting to further study these phenomena and to determine the substances to which the toxicity of the urine is due. Feltz and Ehrmann attribute it to potassium salts, but the analyses which we have made have not enabled us to find any clear relation between the variation of the salts and the changes of the toxicity. Authorities are at present inclined to believe that a toxic rôle is played by ptomains, produced, perhaps, by the microbe of pneumonia. Drs. Lépine and Guérin have found alkaloids in pneumonic urines. By examining 200 cubic centimetres of urine, they found ptomains which when injected into frogs killed them within twenty-four or forty-eight hours. In grave cases they found much more toxic alkaloids. Thus, in one observation the alkaloids of 250 cubic centimetres of urine sufficed to kill a frog in two hours. The most interesting fact, however, is that the day following defervescence they could obtain hardly any toxic bases, even by employing 900 cubic centimetres of urine. Whatever the active substances may be, the urine of pneumonia patients differs from normal urine in that it is highly convulsant and often causes salivation. Normal urine also contains a sialogen substance, but the action of the latter is masked by the other poisons. It must be extracted from the urine, while its presence is manifest in pneumonic urine even when the total urine is injected.

Crisis in Typhus. Next to pneumonia, typhus fever is, perhaps the disease which most clearly terminates by crisis. Its fever chart recalls fairly well that of pneumonia. The rise is sudden, and on the evening of the first day the temperature reaches 102.2° F. (39° C.). During the stationary period the fever oscillates between 102.2° and 105.8° F. (39° and 41° C.). Defervescence is often preceded by a precritical period during which the temperature is slightly reduced. At the moment of crisis, which is effected in twenty-four or forty-eight hours, it often falls below normal. Coinciding with the fall of the temperature there is a complete and truly astonishing modification in the general condition of the patient—stupor disappears, the skin becomes moist, and the sleep sound. Finally, the urine, which was scanty and red, becomes profuse and pale.

Crisis in Erysipelas. Erysipelas is often cited among diseases which terminate by crisis. In fact, there are cases in which defervescence occurs in an abrupt manner as in pneumonia. Between evening and morning the temperature falls from 104° to 98.6° F. (from 40° to 37° C.), not to rise again. Oftener, however, defervescence takes forty-eight hours, either because the temperature is reduced gradually, or because, after a fall to 98.6° F. (37° C.), it once more rises on the evening of the first day, and does not remain normal until after the second day. Finally, the temperature is not infrequently reduced by lysis, presenting a series of variations. Whatever the mode of termination may be, a hypothermic state in which the temperature falls to 96.8° F. (36° C.), sometimes even to 96.4° F. (35° C.), often occurs after defervescence. In two cases we have found 94.7° F. (34.8° C.) in the absence of any notable disturbance.

The study of thermal modifications should be supplemented by investigation of the urinary variations. The researches which we have pursued on this subject, with the assistance of Dr. Marsat,[1] demonstrated that the modifications are analogous to those observed in pneumonia, except that they are less pronounced. During the stationary period the urine is scanty. The amount does not exceed 700 or 900 cubic centimetres, the color being mahogany red. The density rises and varies between 1.022 and 1.030. The reaction is acid. At the moment of convalescence a critical polyuria is produced. The amount voided rises to 1500 and 2000 cubic centi-

[1] Marsat. Essai d'urologie clinique dans l'érysipèle. Thèse de Paris, 1894.

metres. The color is clearer, and the density falls to 1.017 and 1.010. At this time a transitory incontinence of urine which lasts a day or two occasionally occurs in women. The modifications in the urea, phosphates, and chlorides are far less marked and clear than in pneumonia. The *chlorides* diminish, as in pneumonia. Of these from 2 to 6 grams are, however, found during the stationary period. At the moment of convalescence the daily figure rises to 12 and 13 grams. The modifications in the *phosphates* are very irregular. In the majority of cases there is diminution during the stationary period and a return to the normal at the time of convalescence; but the modifications in the phosphates are often produced in a sudden and unexpected way which is not explained.

Crisis in Scarlatina. Among the eruptive fevers scarlatina deserves particular attention. The researches pursued in our laboratory by Dr. Mazaud[1] showed with accuracy the urotoxic variations produced in this infection. At the beginning of scarlatina the urine is scanty. The absolute toxicity is high—*i. e.*, a small amount when injected into animals suffices to cause death. If, however, the volume is taken into account, it is found that the individual eliminates in the twenty-four hours less poison than under normal conditions. When the urine is albuminous it often presents peculiar properties. It gives rise to intestinal movements which are more or less violent and followed by diarrhea. These manifestations are absent when the urine contains no albumin. It is, therefore, probable that the albumins of the stationary period, which are mainly constituted by globulins, possess toxic properties. Whether albuminous or not, the urine at the beginning of the disease is always convulsant. Hence it seems to contain nerve poisons, a fact which is in perfect harmony with the symptoms presented by the patients.

At the moment of recovery a urinary crisis occurs, supervening in most cases on the tenth or eleventh day. The urinary and the urotoxic crisis are effected at about the same time, but the coincidence is not absolute. An interesting fact is that the temperature is always reduced before the urotoxic crisis appears. In scarlatina as well as in pneumonia recovery precedes and explains the crisis.

Crises in Various Infections. Among the other infections terminating by crisis, although less marked and clear than in the preceding examples, variola, varioloid, and mumps may be cited, as well as

[1] Mazaud. Recherches expérimentales sur les variations de la toxicité des urines au cours de la scarletine. Thèse de Paris, 1898.

typhoid fever, which in one-fourth of the cases, according to Prof. Jaccoud, instead of terminating slowly, as is the rule, ends abruptly. We may likewise mention malaria, the crises of which have been well studied by Mossé, Roques, and Lemoine; and recurrent fever, the spirilla of which appears in the blood before the paroxysm and disappear a little before the crisis. Infectious icterus must not be overlooked. Chauffard has thoroughly studied the characters of the urinary crisis in catarrhal icterus. Since the works of Bouchard and of Mossé it is known that primary grave icterus often terminates in recovery and that disappearance of the symptoms coincides with a urinary crisis running a course parallel to the increase in the urine and urea. Another element may at present be added—*i. e.*, urinary toxicity.

Cholera. There is a disease in which crisis occurs in a reverse direction: that is cholera. In the stationary period the temperature is below normal. At the moment of recovery it rises above and sometimes reaches a figure notably above the normal. Thus a febrile, reactionary period develops, sometimes attended by grave manifestations which may impart to the patient a typhoid aspect.

Conclusions. The facts above reported suffice to demonstrate that crisis is the result and not the cause of recovery. It must be considered simply as a process resulting from an exaggeration of normal phenomena. It is established that in a healthy man the elimination of autogenous poisons is not effected in a continuous manner. The urinary secretion varies from one day to another. It follows a tertian and less frequently a quartan type. Then, even in a normal state of things, accumulations and discharges are constantly produced—that is to say, little crises. This is a particular example of a general law. We have already shown that there is no uniform movement in nature, and that all vital acts are remittent. Starting from this physiological fact, we may regard crisis as a natural phenomenon or an exaggeration of the normal type.

On the other hand, it seems to us that the termination of the disease must be attributed to a change occurring in the activity of the infectious agent. Netter and Patella have shown that at the moment of crisis the pneumococci succumb or are attenuated. It is probable that, under the influence of antitoxins, the microbe ceases to elaborate toxins. At the same time the cellular reaction which has terminated in the production of antitoxins must have armed the nervous centres against the effects of impregnation.

When this reactionary process is at an end the nervous centres become indifferent to the toxins which still remain in the economy, and which, as experience demonstrates, are not eliminated until twenty-four hours later. Hence we conclude that the primary phenomenon is a chemical transformation occurring in the organism protecting the cells against the toxins; in other words, rendering the cells capable of enduring the microbic poison as if the organism were vaccinated. Under these conditions the toxic action is no longer exercised. The symptoms disappear, cellular activity is re-established, and elimination of the poisons may be effected. This is the last act of the critical evolution.

Convalescence. When the morbid process seems to have been arrested and recovery established, the organism is not yet completely restored to its normal condition. There is still a last period, termed *convalescence*.

The appetite, which had been suppressed during the disease, reappears, and it is often so marked that it is difficult to prevent the patient from overeating. The temperature often falls below normal. The figures 97.7° and 96.8° F. (36.5° and 36° C.) are not infrequent, and may be observed for a week or more. Emaciation appears or increases, this probably being due to the great amount of waste which is eliminated by the different emunctories, notably through the respiratory apparatus and the kidneys. Then, at the end of a few days, the patient grows fat, his weight often exceeding that noted before the commencement of the disease, and at times he becomes slightly obese. The nervous system having been most affected during the stationary period, therefore returns more slowly to its normal condition. During the first days following recovery, when all the organs are working regularly, the nervous system is still disturbed. The individual is unable to keep on his feet or walk. If an abrupt movement is attempted, dizziness and palpitation are experienced. Now and then a febrile paroxysm occurs, as, for instance, when he happens to read a little too much, or on the occasion of a visit, an emotion, or an exertion of little importance, such as making his toilet. The thermometer then marks 100.4° or 101.3° F. (38° or 38.5° C.). These disturbances, which seem to depend simply upon a lack of equilibrium in the centres of thermal regulation, and not upon an additional infection, are transitory and in no wise disquieting. The nervous manifestations of convalescence, however, are sometimes much more marked than would be

expected in view of the comparatively innocent character of the disease. In this regard nothing is more instructive than influenza. Even after the slight forms which have lasted but a few days, convalescence is very tedious. Weakness, asthenia, and incapacity for work may persist for weeks or months. Finally, some of the symptoms of the stationary period may reappear. A convalescent from typhoid fever will easily have diarrhea. A convalescent from a thoracic affection will, upon the slightest cause, cough and have pain in the side.

Evidently, the duration of convalescence varies according to the nature, type, and gravity of the disease, and also according to the age or previous condition of the subject. Aged individuals and those who are already weakened require more time to be re-established, and it may often be necessary for them to go to the country or to a warm climate.

Convalescence may be interrupted by a variety of accidents. Besides the nervous fevers already referred to, other causes may produce a rise of temperature up to 102.2° or 104° F. (39° or 40° C.). After a day or two the temperature again becomes normal. This is often a process of abortive relapse. The disease, not being well extinguished, recommences and is arrested by means of timely medication or the natural defenses of the organism. In other instances a septicemia is superadded to the primary disease. Some authorities have even maintained that the relapses of typhoid fever should be considered as infections of intestinal origin—*i. e.*, that the alterations of Peyer's patches, by lessening the means of defense, permit the invasion of the economy by the habitual microbes of the alimentary canal.

Febrile paroxysms connected with cutaneous suppurations may also be observed. The alterations of the skin, like those just referred to in the intestine, permit the pus cocci to produce abscesses or boils. At times an infection is produced in other organs. For example, pneumonia may be observed during convalescence from any disease. Lastly, in certain cases febrile paroxysms occur, which are explained by the aggravation of an antecedent chronic infection. For example, in an individual who has suffered for a more or less considerable period with a torpid or slow tuberculosis, and then contracts measles, convalescence does not become duly established after this intercurrent infection. He remains weak and suffering. He has slight fever every night. The symptoms may thus evolve

rapidly toward a fatal termination, or, on the contrary, they may after a certain time be arrested and disappear.

Relapses and Recurrences. Convalescence may also be interrupted by a relapse. In fact, in certain infections relapse is the rule. Such is the case in *recurrent fever*, and a particular form of infectious icterus, improperly called Weil's disease.

Relapse is particularly frequent in typhoid fever, influenza, and bronchopneumonia. It is rare in lobar pneumonia, and exceptional in other infections. Not infrequently it is caused by a fault of the physician or of the patient. Alimentation may have been too rapid or too abundant; the patient may have got up too soon, or exposed himself to cold, and especially to fatigue. It is relatively easy to treat a disease during the stationary period, but at the moment of convalescence the physician is often greatly embarrassed and requires much tact and experience.

Relapse sometimes manifests itself in a slow and progressive manner. More often it appears suddenly, even in the case of typhoid fever. In this disease the temperature reaches 102.2° or 104° F. (39° or 40° C.) on the evening of the first day. In a general way, relapses are less grave and of shorter duration than the primary affection. There are many exceptions to this rule, however, and a relapse may be more prolonged, graver, and even fatal.

In scarlatina we have never observed true relapses. We have observed erythemata of convalescence, which we have already referred to, and which coexist with various infectious manifestations, a knowledge of which singularly elucidates the significance. Such is not the case with measles. At times a child presents a slight eruption attended with slight fever and diarrhea. Measles is diagnosed, the symptoms resolve, and a few days later an eruption, likewise accompanied by catarrh and fever, makes its appearance. This second attack is generally more intense and better characterized than the first. In one case in which the contagion was clearly established the first attack occurred on the seventh day, and the second renewal in due time, namely, on the twelfth day. The first manifestation may, therefore, be considered as a sort of rubeoliform rash; for it seems logical to admit that the eruption occurring at the habitual moment is the true one.

Variola is not a disease in which relapses are observed. It must be noted, however, that in certain instances some new pustules may appear toward the twentieth day, especially upon the soles

of the feet. At all events, they are not numerous, and rapidly disappear.

Relapses have often been observed in diphtheria. Here is a fine example: The patient had been treated by serumtherapy. His angina, which was of a quite serious character, was on the way to recovery, when one morning he found the throat again covered with pseudomembranes containing a large number of Loeffler's bacilli. Although this patient had already received 60 c.c. of serum, we gave two new injections of 30 c.c. each. The false membranes were detached in four days, but the patient died from diphtheritic paralysis.

Recurrences. A distinction has justly been established between relapse and recurrence. *Relapse* means a new beginning of a disease without a new infection. *Recurrence* is connected with a new infection. In a good many cases the distinction is easy. When a person is attacked with typhoid fever or erysipelas after an interval of fifteen or twenty years, such is evidently a case of recurrence. When, however, the symptoms reappear at an early period, interpretation becomes extremely difficult. Some individuals, particularly women, have erysipelas every month. Is such a case an example of recurrence or of a relapse? It is impossible to answer, since we do not know what period of time is required for the destruction of the germ.

The present tendency is to increase the importance of relapses at the expense of recurrences, and to admit that the microbes remain inactive in the organs and tissues, but ever ready to assume the offensive upon the slightest occasional cause. Indeed, it has even been asserted that in most cases the recurrences of gonorrhea are but relapses. In fact, the gonococcus persists during an almost indefinite period of time in the urethra which it has once invaded. Erysipelas and pneumonia are among the diseases which seem truly capable of frequent recurrences. Recurrences of measles are quite common; those of typhoid fever, smallpox, and scarlatina are very rare. According to the information furnished by our patients, recurrences of measles are observed in 14 per cent. of the cases in adults; that of scarlatina is encountered once in a hundred cases. As to syphilis, recurrence is altogether exceptional. Most of the cases cited as examples of second chancre are accounted for by a confusion with tertiary lesions of the genitals, which sometimes simulate a primary lesion.

Passage of Acute Infections to a Chronic Condition. Although recovery is the normal termination of infectious diseases, there are certain cases in which the evolution is prolonged beyond the usual limits. The disease is then said to have become chronic.

The duration of acute diseases has been arbitrarily fixed at forty days. Beyond this term chronicity is supposed to be established. If the question be considered from a higher standpoint it will be recognized that an essential difference between the two processes is furnished by the study of the evolution. Acute disease is a morbid process in a state of continuous modification. Each day brings about a change which, though often but slightly marked, can nevertheless be recognized by a careful examination. It will then be noted that the organism is reacting—that is, struggling with all its forces to arrest and destroy the morbific cause; it is in revolt against the invader. In a chronic disease the organism submits to the yoke of the pathogenic agent, and seems to have no other ambition than to live with it. It hardly tries to circumscribe its progress. It abandons itself, being incapable of continuing the battle. The reason the condition of the patient is not more quickly reduced is that the invader itself has become less active and aggressive. In this manner a tacit agreement, as it were, is made between the microbe and the organism, and the disease persists, undergoing only extremely slow changes.

Therefore, an acute disease is distinguished by a lively and not infrequently by a too energetic reaction. A chronic disease is characterized by the absence, inefficiency, or the slowness of reaction.

At times, however, the organism may for a moment recover its energy. The result is acute attacks, often occurring without any appreciable cause, and at times as a consequence of exposure to cold, traumatism, or an intercurrent infection. Under these conditions the pathogenic microbe makes a fresh attack, with the result that the organism shakes off its torpidity. This acute spell may be illy directed, undisciplined, and precipitate the morbid evolution, and thus rapidly terminate in death. In other instances, after having given rise to painful symptoms, it leads the organism to recovery. A rebellious gonorrhea, for example, has been seen to disappear after a new acute attack.

Medicine has attempted to imitate these natural procedures. Irritant local applications may realize this indication. Koch's

tuberculin does not act otherwise. It whips, so to say, the torpid evolution of chronic tuberculosis.

An acute process may become chronic without the production of any notable changes. It stops at a given moment of its course. This may occur at the moment of aggravation as well as at the time of improvement of the disease. The violent manifestations subside, the reactions and pains cease, and in certain cases the symptoms are so slight as to lead the patient to the belief that he is cured. Illustrations abound. They are drawn mostly from cases of non-specific infections, mainly inflammations of organs—*e. g.*, enteritis, nephritis, and cystitis, which gradually pass into a chronic condition; also various commonplace or specific suppurations. Gonorrheal urethritis, for instance, is thus transformed, and often persists during an entire lifetime, occasioning no disturbance, and unknown even to the patient. Finally, of the specific infections, we must especially mention tuberculosis, which, after an acute attack, may follow a slow evolution.

In order to more closely study the evolution of chronic lesions let us consider an abscess somewhat deeply situated. In its development it produces various disturbances; then, when it is opened to the exterior, the symptoms cease. Suppuration, which is at first very abundant, diminishes progressively. An early recovery may be expected. At a certain moment, however, improvement is arrested, and a fistula discharging a seropurulent fluid is established. There is no longer any general or local reaction. This lesion, which becomes chronic, is borne by the organism without any apparent inconvenience. However, at the moment when chronicity is established, the discharge undergoes some modifications. It loses its freely purulent character; it becomes more serous and more mucoid, and at the same time the microbes diminish in number and virulence. Failure to recover in such instances is often due to the presence of a foreign body, a splinter, or a sequestrum in the focus; or else there is diseased tissue at the bottom of the fistula. When it is possible to intervene and extirpate or remove this inflammatory body, the organism triumphs over the bacteria and the lesion heals. Thus foreign bodies, although absolutely harmless when they are aseptic, maintain an infection which would be cured in their absence. This is a remarkable example of pathogenic association.

The microbe, although attenuated, is not absolutely inoffensive in such chronic conditions. It seems even that its feeble pathogenic

potency depends mainly upon some protective power exerted by the wall of the morbid focus. Chauveau has shown that the pus of a seton which produces no disturbance is virulent. If a particle of it be inoculated into another point of the economy, disturbances are produced. The pus was endured only in its old focus.

In cases of chronic suppuration fistulæ may from time to time become occluded. The subjacent focus is then filled with pus and increases in volume; it becomes painful and gives rise to fever. After an artificial or natural opening the lesion resumes its slow and chronic course. In other instances the fistula becomes closed; it appears to be healed, as no symptom is any longer apparent. For months or years the lesion gives rise to no disturbance whatever; then the focus, which seemed extinguished, is again kindled and a new attack is produced. Such a course is produced especially in cases of osteomyelitis, where a sequestrum may give rise to very tardy disturbances at considerable intervals. The microbe slumbers for years as an absolutely inoffensive guest. An occasional, often unnoticeable, cause enables it to recover a certain degree of virulence and to arouse inflammatory reactions.

A similar evolution is sometimes observed after typhoid fever. This disease never passes into a chronic state, but the microbe that causes it may become localized at certain points, notably in the bone-marrow, and thus call forth a slow inflammation which terminates, after several months, in a focus of osteomyelitis. Bacteriological examination demonstrates the presence of Eberth's bacillus therein. In this case the acute disease ends in a chronic process quite different from what it had originally been.

We can find highly interesting illustrations in the history of ulcers. Let us consider, for example, the varicose ulcer. A slight lesion, an abscess, a pustule, a simple abrasion having induced an infection so mild that no symptom is produced, and the existence of which we admit simply by induction, is the starting point. Reparation is not effected because the tissues were altered. Their nutrition was profoundly disturbed by the varicose condition of the veins. The skin had become hard, brownish, and sometimes the seat of eczema. Therefore, the little lesion sufficed to produce a chronic affection in the suffering tissue. The same explanation is applicable to ulcerating dermosynovitis. This is a trophic lesion induced by an ordinary cause or a slight infection, and it develops and persists because nutrition is profoundly disturbed by nervous lesions.

Experimentation confirms the data of clinical observation by demonstrating that section of sensory nerves hinders considerably the process of repair. For example, division of the sciatic nerve in a guinea-pig is often followed by ulcerations in the foot operated upon; but if care be taken to protect the limb by means of a sort of plaster shoe, infection is prevented, and no nutritive disturbance appears.

The same is true of ulcers of mucous membranes. A commonplace lesion, in most cases of infectious origin, may serve as a starting point for an ulcer of the esophagus, duodenum, and especially of the stomach. Ulcer of the stomach develops in hyperchlorhydric dyspeptics. The excess of acid hinders reparation. Filhene has given an experimental demonstration of this pathogenesis: Two rabbits received considerable doses of arsenic subcutaneously. In one of them, kept as a control, gastric ulcers developed; in another, to which bicarbonate of soda was administered to neutralize the gastric juice, no lesion was produced.

Although the organism plays a very important part in the development of ulcers, we must recognize that the lesion is sometimes dependent upon the nature of the pathogenic agent, its degree of virulence, and the point at which it is developed. The ulcerations of tuberculosis, glanders, and syphilis and phagedenic lesions belong to this group. The influence of the organism, without being absolutely null, is in such cases considerably reduced.

An acute lesion may pass into a chronic state under a form relatively favorable, namely, *induration*. In such instances the organism succeeds in completely destroying the pathogenic agent, but the ulcerations produced are too profound to admit of perfect reparation. The tissue, instead of returning to its primary condition, is replaced by a newly formed fibrous production. This termination is observed in superficial lesions, in certain abscesses, and in adenopathies; but it is particularly important in deeply situated tissues and organs. In this manner cicatrices are produced which, when located in the mucous membranes, cause deformity and embarrass their normal action. When located in such passages as the esophagus or the urethra they result in stricture; in the viscera, such as the heart, liver, or kidneys, they produce sclerosis. In these cases the chronic process differs completely from the acute. As we have shown in treating of sclerosis, the process of repair remedies the first disturbances, but creates a hinderance to the regular activity of the organs.

The chronic processes, the mechanism of which we have indicated above, undergo no modification or evolve slowly either toward recovery or toward death. In both instances changes ending in one or the other of these two terminations are produced either in an insidious manner, or else the chronic course is interrupted by an acute attack which leads, as the case may be, to recovery or to death, or, as a third alternative, leaves the organism in the same condition as before its occurrence.

Death. When an acute disease ends in death the fatal termination may occur suddenly, in an unexpected manner, or slowly and progressively, preceded by more or less prolonged agony. If necropsy is performed, macroscopic or microscopic lesions are sometimes found. In other cases post-mortem examination gives a negative result. By taking into account the various results which may be obtained the causes of death may be divided into three groups: 1. Mechanical disorders or barriers. 2. Lesions of an important organ. 3. General infection or intoxication.

As a striking illustration of the mechanism of death by a mechanical cause we may mention diphtheritic laryngitis. The pseudomembrane developing in the larynx embarrasses the passage of air, and may cause death, partly through the reflex spasm which it excites. Likewise, a phlegmon taking its origin in certain regions, may, by its size or by the edema surrounding it, mechanically induce a fatal termination. In these examples death evidently results from the obstacle created by the lesion, since if the false membrane be detached or the circulation of air be re-established through intubation or tracheotomy, or the phlegmon be opened, the disorders disappear immediately.

The local lesion which thus endangers life is not, however, the work of a microbe, but is due to a reaction of the organism, which seems to fight against itself. But if we more closely investigate the succession of the phenomena, we understand that the organism has produced a false membrane or a purulent focus in order to prevent general impregnation. The lesion thus created was designed to circumscribe the morbid process and to oppose the penetration of microbes or their toxins. The organism, however, is not always capable of proportioning its efforts to the work required. In a good many instances reaction exceeds the end. A microbe penetrating into the lungs induces an acute pulmonary congestion. The vessels dilate in order to facilitate the escape of fluids and cells which will

arrest the development of the parasite. The reactionary phenomena, however, are often too intense, and may induce grave accidents. In other cases the microbe reaches the surface of the lung and irritates the pleura, which then secretes a fluid that is often so excessive in amount as to necessitate surgical intervention for its evacuation. Lastly, in certain instances reaction is not too strong. It is truly beneficial, but it is produced in particularly delicate localities, and for that reason may prove dangerous. Such, for example, are congestion, edema, and abscess produced in the brain. Under these various conditions the organism endeavors to remedy the immediate disorders, but it mobilizes too great a number of cells or gives issue to an excessive amount of fluid.

Under such circumstances, therefore, therapeutic measures should be directed to the organism itself, so as to moderate the morbid reaction and check the intense congestion which threatens to give rise to asphyxia by reason of its intensity. In other instances, on the contrary, we must assist the organism in its efforts to accomplish that part of its work which it is unable to do alone. Puncture of a pleural collection or the evacuation of a cerebral abscess is not medication against nature, but a complementary method aiding the insufficiency of natural means.

As morbid reactions may, on the one hand, endanger life by their excessive intensity, on the other, their insufficiency may be a new cause of disorders. When a microbe develops it gives rise to substances which destroy the surrounding cells. The destroyed elements are liquefied and, when possible, thrown out. When the organism fails to remedy the imminent accidents by the various means at its disposal, notably through the accumulation of wandering cells, or if the leucocytes be killed as they arrive at the point of invasion, a more or less complete destruction of the affected tissue will result. Gradually extending, necrobiosis may reach a vessel, and, if the course of the process is rapid, a grave or fatal hemorrhage occurs before a clot is formed. In other cases an important cavity is opened. For instance, the wall of the intestine may be perforated. In these various instances lesions which are apparently sufficient to account for death are revealed by the necropsy.

As a result of anatomico-pathological discoveries we have become so accustomed to attach an exaggerated importance to anatomical lesions that our minds are satisfied when the necropsy detects a morbid focus in some important organ. Let us take, for example,

the case of a child dead of measles. During life a murmur was found at the base of one lung, and on opening the cadaver a focus of bronchopneumonia is discovered at this point. The mechanism of death in this instance appears to be readily conceivable; yet on a little reflection, it will be acknowledged that it is hardly possible to attribute the fatal termination to a lesion so small as not to hinder hematosis to any great degree. The same reasoning is applicable to other organs as well in those cases in which multiple lesions are found. In acute miliary tuberculosis, when the tubercles have invaded the serous system only, why has the individual died? Pushing the question further, it may be asked: Why has he succumbed even when the multiple granules have invaded the viscera? There generally remains sufficient intact parenchyma to assure the function of the organ. It is here that modern science intervenes and rightly proclaims the rôle of toxins secreted in the diseased organs and leads to the admission that death is due to poisoning. This interpretation is confirmed by those cases in which no manifest lesions are revealed by the necropsy.

Let us suppose an individual succumbing to anthrax. The blood is disintegrated, dark, and sticky, and the spleen is voluminous and the other viscera congested. At times small visceral ecchymoses only are met with. This is evidently somewhat disappointing. On examining, however, a drop of the blood or a particle of the organs under the microscope, innumerable bacilli are observed, and thus some light is shed on the problem. Death is due to general infection. Toussaint used to say it was due to an obstruction of the capillaries by the bacilli. But this invasion and dissemination of the foreign elements does not seem to be sufficient to explain the fatal termination. It is neither by crowding the vessels nor by abstraction of oxygen or of the materials necessary for cellular renovation that the bacteria have destroyed life, but by secreting soluble substances capable of disturbing the activity of the cells.

This interpretation, which may seem contestable as regards anthrax, is the only one admissible in reference to those diseases the pathogenic agent of which is localized at a certain point of the organism. In diphtheria, gaseous gangrene, and cholera the microbes do not invade the economy. They remain localized at a point or confined to the digestive canal. Death cannot, therefore, be attributed to any other cause than the soluble substances engendered by the micro-organisms.

It is not enough, however, to say that death is the result of an intoxication. We must endeavor to indicate more accurately the mechanism of a fatal termination. In certain cases lesions are found which of themselves would be sufficient to endanger life. For example, the autopsy reveals degeneration of the liver and kidneys, myocarditis, or hemorrhages of the suprarenal capsules. Chemical analysis shows the diminution or even the absence of glycogen in the liver, and microscopical examination demonstrates the presence of cellular lesions in most of the organs. It may then be asked whether these multiform alterations have not played a part in bringing about the final result and whether the autointoxication arising from organic insufficiency has not been added to the microbic intoxication. This, however, would only displace the problem, for it is at all events to be recognized that the cellular lesions are, in certain cases, too limited to exert a notable influence. We are thus brought again to admit a toxic action. This action, however, is not immediate. The microbic poisons do not kill rapidly, but a certain length of time elapses between the moment of their introduction and the instant when the first responsive manifestations appear. Instead of at once arresting the nutritive activity which essentially characterizes life, the microbic toxins disturb nutrition by adulterating the intercellular medium. Whether the poison itself modifies this medium, or whether the secondary products originating under the influence of the toxins act as a ferment, is a matter of little importance. What is an important fact, however, is that even when a fatal dose is at once introduced into a vein, the animal dies only after the lapse of several hours. This means that a whole series of secondary modifications are produced through the influence of the toxin.

We are thus led to consider not the total death, but the individual death of the parts of the organism—*i. e.*, of the cells. It might be supposed that, under the influence of toxins, nutrition is equally perverted in all parts of the organism; but such a conception is hardly admissible. The cells are disturbed according to a fairly determined order—those performing the highest functions are affected first. The nerve cells occupy the highest position, and experimentation in accordance with clinical facts shows that it is upon them that the deleterious action of toxins is in most cases exerted. The dynamic state of the nerve cells being thus modified, it is comprehensible that an occasional cause, by producing in them an abnormal agitation, may induce sudden or speedy death. Other-

wise, the fatal termination supervenes gradually as the result of progressive weakening of metabolism. In order to admit these different conceptions without reservation we should be exactly informed as to the functional state of the various parts of the organism at the moment of death. Here is a most difficult question which has not as yet been the subject of experimental studies.

In brief, death as a result of infection is death from intoxication. The microbic poisons accumulate in the organism and hinder or prevent normal cellular life. Possibly they act by forming combinations with the cellular protoplasm. It is more probable, however, that they affect the cells by adulterating the intercellular medium. The result is a series of functional disturbances which cause death, and at the necropsy no lesion, or almost none, is found even under the microscope. If lesions are met with they are too small to account for the fatal termination. If life is prolonged, however, functional disorders induce anatomical modifications. Thus important cellular lesions are secondarily produced which play an important rôle in the mechanism of deferred death. Here, however, the question is no longer one of infection, but of organic lesions evolving on their own account and deriving no particular character from their origin.

It is well here to call attention to a mode of termination which is not rare in young children and the aged. The patients recover from their infection and seem to be entering upon convalescence. Such is not the case, however; general debility rapidly progresses, and emaciation becomes more pronounced day after day. Then the intelligence becomes dull; eschars make their appearance, and at times slight fever manifests itself in the evening. After a period of time, varying from eight to fifteen days, death supervenes without any other symptom, as a result of post-infectious cachexia. Such an evolution is observed after erysipelas. We may, in this connection, report the case of a man, sixty years of age, who entered our hospital for an erysipelas of the face on the twentieth day of its evolution. On the day of admission his cutaneous inflammation still occupied the nose, forehead, cheeks, eyelids and scalp. The temperature was 103.5° F. (39.8° C.), accompanied by slight delirium. The urine contained no albumin, the liver was not swollen. Two days after the temperature fell to 101.7° F. (38.5° C.), and five days after his admission it returned to normal. He seemed to have recovered from the erysipelas, but his general state remained quite

unsatisfactory. The temperature continued to fluctuate about 98.5° F. (37° C.), and he was becoming cachectic quite rapidly, and thirteen days after his admission he died. For the last eight days his temperature had been normal, and on the day of death it was only 98.5° F. (36.6° C.). The necropsy revealed no special lesion capable of explaining the fatal termination. The lungs, particularly the right lung, were congested at the bases. The heart presented a slight fatty condition. The mitral valve was thickened, the aorta slightly dilated and atheromatous. The kidneys were also surrounded with a thick layer of fat. The liver presented the color of chamois leather, and on section, violet. The weight of all these organs was less than normal. The cause of this post-infectious cachexia is probably chargeable to a previous insufficiency of the organs concerned in the protection of the organism against infections, notably the kidneys and the liver. The toxins elaborated by the pathogenic microbe are not destroyed or eliminated with gratifying rapidity; hence impregnation is more profound than is indicated by the benign character of the infectious lesion, and its effects continue after apparent recovery. The situation is the same as in certain animals brutally inoculated with a large dose of an attenuated microbe. If the microbe is highly virulent, the animal dies from an acute septicemia. If moderately virulent, it is destroyed, but the toxins which are introduced with the pathogenic agent and those which are elaborated by it within the organism continue their action and give rise to a fatal cachexia. This is what happens notably with the streptococcus. In fact, we have shown that intravenous injection of attenuated cultures seems to produce no symptoms, and then, after a few days, the animals grow thin and succumb in from fifteen to twenty or thirty days after the inoculation, in a state of an extraordinary degree of cachexia and emaciation. At this moment the microbe has disappeared from the organism and cultures made from the organs remain sterile.

CHAPTER XVIII.

THE CONSEQUENCES OF INFECTION.

Apparent and Real Recovery. Reparation of Traumatic Lesions and of Toxic-infectious Lesions. Comparison between These Two Processes. Causes of the Differences. Post-infectious Visceropathies. Their Mechanism. Their Evolution. Epithelial and Interstitial Visceropathies. Importance of Visceral Scleroses. Significance of Scleroses.

Can an infection be cured completely? The disease having terminated, can the organism return to its former state? Can all the disorders that were produced disappear and all the lesions be repaired? From a practical standpoint there is no doubt as to the answer to this question. After an infection, even though it be grave or prolonged, health is re-established; the patient is conscious of having returned to his normal state; years may elapse, and life may come to an end without the slightest manifestation having been observed which might rightly be traced to the previous infection. If, however, the question be considered from a higher point of view a quite different solution is reached. Complete restoration of the economy to its previous state seems to us impossible. Recovery being due to modifications in the fluids and the fluids being cellular secretions, it is, of course, necessary for changes to be produced in the mode of life—*i. e.*, in the nutrition of the cells, in order that the infection may be overcome. If at all possible, the return of the organism to its normal nutritive mode is to be gradually effected. Will such be the case in every instance? Observation teaches us that, in a great number of cases, nutrition is profoundly and definitely modified. The variations in the degree of fatness of the individuals are, from this standpoint, quite demonstrative. In some cases obesity, in others an excessive emaciation, is the permanent result following an infectious disease. These changes are readily appreciable after acute infections, such as typhoid fever, or even after recovery from a chronic infection such as tuberculosis. In some of these cases the post-infectious modifications are favorable. The infection having, so to say, whipped the organism to greater activity, improves the health, with the result that certain ill-deter-

mined disturbances, often attributed to diathetic conditions, disappear, and previous chronic, notably nervous, affections are cured. The reverse effect, however, is unfortunately more frequent. The acute disease often proves to be the occasional cause of a series of consecutive disturbances and various neuroses. In certain cases the consequences of infection are so pronounced as to be noticeable even by the most superficial observers. Not infrequently, however, they easily escape notice and are very difficult of interpretation. As a matter of fact, these consecutive changes are sometimes so slight that we are compelled to assume their existence by induction rather than by observation. Moreover, they may make their appearance very tardily; months and years elapse, and when symptoms become apparent after such long periods some hesitation is felt in connecting them with their true cause.

We must now successively consider the consequences of local lesions produced by toxins and general disturbances which may develop under their influence. The local action of toxins is expressed, as is known, by degenerations or cellular necrobioses. The most clearly differentiated elements, which perform the highest functions but which are also the most delicate, are first attacked. The cells constituting the tissues and organs are not all similar. All of them do not have the same force of resistance; hence, in the presence of the same morbific cause, they do not all react in the same manner. Certain cells succumb, while some undergo alterations, some remain intact, and still others present evident signs of excitation and may abundantly proliferate. The ulterior fate of the organ differs according to the state of these variously affected cells. Those which have begun to proliferate may serve to repair and replace those which, being less resistant, have degenerated or been killed. A perfect reparation might, therefore, be expected. In reality, however, such is not the case. There is a curious difference between the reparation of traumatic and of infectious lesions. When a part of an organ is excised, complete restoration is possible. Let us suppose that even a large piece of the liver is cut off. If the experiment is well conducted, if infection is avoided, repair will be effected and newly formed cellular tissue will fill up the deficit. If, on the contrary, the cellular destruction is the work of infection, reparation will not be as complete. A great number of the diseased cells will be replaced not by similar cells, but by sclerotic tissue. Microbic as well as exogenic poisons are capable

of exerting the same influence. If very small doses of phosphorus are administered to an animal, degeneration of its hepatic cells is produced. If the employment of the poison is then stopped, cicatrization takes place—*i. e.*, a proliferation of connective tissue, which replaces the dead cells.

Not infrequently, however, infection as well as intoxication destroys only a small number of cells. Their replacement would, therefore, seem easier than in cases in which traumatism has caused the disappearance of one-fourth or one-third of the gland. Is it not also known that extirpated organs have completely regenerated when a small fragment had been left? In such cases reproduction of nearly all the cells and of the primary type has taken place, although the task of reparation seemed far more difficult than in the case in which destruction is partial and disseminated. This fact proves that sclerosis is not, as might have been believed, a tissue taking the place of destroyed cells. It is necessary that this destruction should present certain particular characters. This fact may eventually be interpreted in several ways. The simplest explanation seems to be the following: In the case of traumatism the excised cells are far more numerous, but the remaining cells are sound; they possess normal activity; they proliferate and occupy the place left vacant. On the other hand, in the case of infection—and what we say of infection is applicable to intoxication—the soluble substances impregnate the whole gland. The cells which first receive the poison or those which are less resistant, degenerate or are killed; others, although they survive and are apparently normal, do not, however, completely escape the influence of the morbific cause. Their activity is, therefore, disturbed, and, although the modification is not expressed by any lesion appreciable under the microscope, it is safe to assume that this modification is sufficient to hinder proliferation. It is thus conceivable that reparation is the more difficult and incomplete the more profound is infection. We may repeat once more: sclerosis is produced not because the destroyed cells are too large in number (infection never causes the disappearance of as many of them as does traumatism), it occurs simply because the remaining cells are not normal. The same interpretation is applicable to those cases in which the focus of destruction is well limited. The neighboring cells are alone disturbed, but these are precisely the cells which should proliferate and are incapable of so doing. It is, therefore, intelligible that an infectious lesion,

however small, may produce more extensive disorders than a far more considerable traumatic lesion. The result is that reparation is less perfect.

If the lesion is well localized and not very extensive, the resulting cicatrices may sometimes produce no disturbance. Such is not always the case, however, as may be seen from the frequency of strictures occurring in the urethra in consequence of gonorrhea. This illustration elucidates the history of organic lesions. Visceropathies have long been considered as diseases. Imbued with the false idea of morbid spontaneousness, physicians believed they had solved the nosological problem when they found a cardiac, renal, hepatic, or cerebral lesion. For instance, a mitral insufficiency was detected, and if rheumatism was not found in the antecedents of the patient, no investigation was made as to the cause of the lesion. At present we know that every disease is caused by an external agent and that visceral lesions are nothing else than the consequences of previous diseases. The process occurring in the organs, though of a more complex character, is none the less comparable to that occurring in the urethra.

The pathological anatomy of acute infections has shown us that cellular lesions are far more intense and diffuse than was once believed. The systematic study pursued in recent years with regard to the viscera and the tissues during infections leads us to the question how any process of repair, even incomplete, is still possible. It is true that when visceral lesions are too extensive, death supervenes during the acute stage of the disease, and less frequently it occurs after the process seems to be at an end. We have already shown how the aged thus succumb to a post-infectious cachexia. At a less advanced stage, however, a return to health seems to be effected. The most careful examination reveals no appreciable disorder, and, for a number of years, the organism seems to have returned to a perfectly sound state. Nevertheless, a silent evolution is going on, ending in visceral sclerosis. The lesion may exist for a very long period of time without being expressed by any symptom. This is owing to the fact that the organs contain a far greater number of cells than is necessary for life. It may be assumed that 40 to 50 per cent. of the glandular tissues may be suppressed without bringing about any disturbance. One-third of the liver, a whole kidney, even a whole lung, may be extirpated without great inconvenience. It is therefore intelligible that a visceral lesion may evolve during years

without producing any symptom. The affection is in a state of latency, and will be revealed later, either by signs detected by methodic exploration or by the fact that the unstable equilibrium of the sanitary condition resulting from the visceropathy is disturbed by some intercurrent and maybe unimportant cause. The symptoms may thus make their appearance suddenly or progressively on the occasion of a cold, traumatism, fatigue, an error of diet, or a new infection. It must also be remembered that, in certain cases, the visceral affection always remains in a state of latency, and will be disclosed only at the necropsy. In other instances the visceral affection is revealed in a sudden manner, causing sudden death.

The necropsy in such cases surprises the physician by revealing profound lesions which had remained so long in a state of latency without manifesting any clinical disturbances.

The organic affections which appear thus as the consequence notably of previous infectious diseases, may be divided into two great classes. In one of them epithelial lesions predominate; in the other, sclerotic lesions. Hence, the classical division of affections into parenchymatous and interstitial, a division which seems to be justified both by clinical observation and pathological anatomy. On investigating, however, the causes which have led to the development of these two distinct processes, we find the same etiology and the same infections responsible for both kinds of changes. We are thus led to the idea that visceral lesions are everywhere and always at first characterized by a diffuse inflammation, and this idea finds a solid basis in anatomico-pathological studies. In view of the facts hitherto reported, we reach the conclusion that microbic toxins first give rise to epithelial degeneration, which is soon followed by inflammatory, epithelial, and interstitial reactions. At this moment the process is diffuse. Later, when the acute phenomena have passed, a chronic evolution takes place in either direction. One of the elements predominates, and the result of the processes which were at first identical, is either a parenchymatous or a sclerotic inflammation. It is more difficult to determine the causes which intervene and direct the anatomical evolution. Two factors, as always, may be admitted: the toxins induce degenerative or simply irritative lesions—*i. e.*, cause the death of the highly organized cells or stimulate the proliferation, according to (*a*) the degree of resistance of the subject, or (*b*) the degree of activity of the microbe. It is conceivable that, in the former instance, the elements that are killed

may not be replaced by any other than connective tissue. In the latter case, on the contrary, the perishing cells are smaller in number and the vacancies left are filled up by the neighboring cells the activity of which is increased. Reparation would therefore be perfect if there was only cellular hyperactivity. But pathologic histology establishes that along with this overactivity there is a nutritive deviation. In this connection our researches concerning the modifications of the thyroid gland are quite demonstrative. We have shown that, in the most varied infections, the following three phenomena are always present: death of some cells and degeneration or increased activity of certain others. In some cases the two last processes coexist; the nucleus is multiplied while the protoplasm degenerates. But the modification of the secreted fluid proves the profound disorder of the cells. Colloid matter presents reactions which enable us to follow under the microscope the histochemical changes occurring in it. It is very easy to thus prove the functional disturbances. It is therefore conceivable that when the infection is terminated, three different processes may ensue: In some cases degeneration will predominate, in others proliferative overactivity, and in still other cases sclerosis will replace the dead elements. In the last instance the process has been too intense; the cells in the neighborhood of those that have succumbed are themselves too much affected to proliferate and occupy their place. Sclerosis, therefore, seems to us to be the termination of intense, extensive, or prolonged inflammatory processes. Let us again take urethral stricture as an example. In cases of gonorrhea occurring only once and having been rapidly cured, stricture is exceptional. The cells adjacent to those destroyed have succeeded in taking the place of the dead. In gonorrheas of long duration stricture is the rule, since the cells destroyed are too large in number, and those surrounding them are too deeply affected to establish normal relations. A cicatrix, that is, sclerotic tissue, is, therefore, produced.

The sclerotic tissue destined to fill up the vacancies left by the dead cells must be considered as a tissue of replacement. Whether it be developed, as is generally held to be the case, at the expense of the cells of connective tissue, or is progressively produced by hypertrophy of pre-existing fibres, as seems to be the case in certain instances, it is always destined to remedy immediate accidents. This sufficiently indicates that we reject the existence of primary scleroses. The connective tissue alteration is always preceded by a

lesion of the more highly differentiated elements. In other words, scleroses are always of epithelial origin. Let us consider an organ in which scleroses have often been studied, for example the kidney. An attempt was made to admit two kinds of nephrites, namely, epithelial and interstitial, the latter indicating sclerosis from the first. A special etiology, pathogenesis, and symptomatology had been assigned to each of these two affections. A change was little by little produced in this conception. It was recognized that every case of nephritis begins in the more highly organized elements and that the process soon extends; so that nephritis is primarily diffuse, and later on evolves toward various anatomico-clinical types, the two extremes of which are represented by the large white kidney, in which the epithelial lesions predominate, and by the small red kidney, in which the sclerotic lesions prevail. Thus are constituted sharply distinguished affections which must be separated in anatomical and clinical descriptions. The point of departure, however, is the same in all. The final result differs because all organisms are not similar.

The same conception is applicable to hepatic cirrhoses. The origin must be looked for in a primary lesion of the hepatic or the biliary cells. The idea of connecting atrophic cirrhosis with a primary alteration of the portal vein, which is still held by some authorities, is based upon incomplete anatomical study. It is at present demonstrated that the process is not as systematic as was once believed. Sclerosis develops simultaneously around the portal and suprahepatic veins and forms bands so irregular as to defy all topographical description. On the other hand, a sclerotic lesion is never seen to diffuse toward adjacent parts. It is, therefore, probable that poisons or microbes circulating in the portal vein produce primary alterations in the hepatic cells. The marginal cells are the most profoundly influenced and the first to be affected; next the central cells, which the blood reaches after passing through the capillaries. Thus the topography of the sclerotic lesions is explained. In most cases the venous alterations seem to be of a secondary character. It must, however, be admitted that they may sometimes be primary. They may then produce sclerosis, because the circulatory disorders disturb the nutrition of the cells. Even in these cases the sclerotic process is not an irradiation of the periphlebitis. It is consecutive to a degenerative alteration of the hepatic cells.

It would be easy to present analogous considerations in reference to other glands and various tissues, and thus show that sclerosis is always designed to fill up vacancies.

Sclerosis of the nervous tissue seemed, for a time, to be an exception. In reality there has been an error of interpretation in this matter. It is at present known that scleroses of the neuroglia do not enter into the group of true scleroses. The neuroglia does not represent connective tissue. It is an ectodermic production, a nervous tissue. It is not strange if systematic lesions not obeying the rules above reported are produced in this tissue. The process is a special one quite different from true or mesodermic sclerosis.

Although infectious diseases influence the entire economy, the lesions resulting from this influence must be diffuse. Generalized sclerosis affecting the tissues and viscera are observed in certain instances. The *ensemble* of these facts is known under the name of arteriosclerosis. With or without good reason, a predominating part is thus attributed to the arterial system in the genesis of these disorders. The conception is not groundless. The microbic toxins carried by the blood current must first impregnate the vascular walls. Even when arteriosclerosis is generalized, however, it predominates at certain points. Hence a cardio-aortic, a renal, and a cerebral sclerosis have been described. Finally, in a certain number of cases, the process seems to be different, although I hold it to be of the same order; the arteries are slightly, if at all, affected; a single viscus is injured. This single visceral sclerosis must be classed with multiple organic sclerosis. It is always the same process, progressing in an identical manner and depending upon a similar cause. It is in all cases the result of toxi-infection. It is intelligible, however, that the morbid localizations and post-infectious sequels may differ according to the intensity of the infectious process, the responsive aptitudes, and the inborn or acquired predisposition of the individual. This is sufficient indication that we do not class visceral scleroses with arteriosclerosis. We believe that the two orders of lesions progressing side by side depend upon a common cause. Sclerosis of the arteries and that of the viscera are two simultaneous effects of the same cause. The bond existing between arteriosclerosis and visceral scleroses is not one of subordination of the latter to the former. The frequency of this association is due to the action of the same cause upon similar tissues. To isolate the arterial alterations from the entire process in order to make of

these the cause of visceral alterations is to make an artificial dissociation which is in nowise necessary for explaining the pathogenesis of these lesions.

Scleroses, whether arterial or visceral, may begin in childhood on the occasion of a first infectious disease or simple digestive disturbances the importance of which is just being appreciated. The numerous fermentations which so easily occur in nurslings produce alterations in the entire organism, and may evidently become the starting point of a number of organic affections the origin of which often remains undiscovered. It is conceivable, however, that scleroses become more frequent as the individual advances in age. The aged are almost always affected by it. It is quite difficult, however, to determine the part due to the infection. Visceral or arterial scleroses are the termination of all pathogenic causes which have acted upon the organism and which are almost always multiple. Exogenic intoxications (alcoholism, saturnism) and endogenic intoxications (autointoxications) are superadded to infectious intoxications and give rise to alterations which end in sclerosis. The organic lesion thus constituted preserves no character of its origin. On the contrary, it acquires a perfect autonomy, progresses on its own account, and in its turn engenders disorders which are always the same regardless of their point of departure. This is the reason why physicians have long believed in the existence of diseases of the organs when in reality they were nothing more than organic affections, more or less tardy consequences of previous diseases.

It is thus intelligible that the history of the consequences of infections may be at times of greater importance than the history of the infections themselves. Anything that is known as diseases of organs may be the tardy consequence of an infectious process. The reason visceropathies are not more serious and frequent is that the means of defense and of compensation at the disposal of the organism are extremely numerous.

If we consider in their entirety the modifications produced by infection in organs and tissues we see that it is possible to classify them under three headings: modifications expressing increased functional activity; modifications in the structure of the cellular elements and modifications in texture—*i. e.*, changes in their mutual ordination.

Increased functional activity represents a return of the organism to a former state of its evolution. It is a kind of rejuvenation which

is particularly appreciable in the bone-marrow, but which is no less manifest when chemical analysis is applied to other tissues. Infection thus arouses functions which seem to be extinct. But this favorable occurrence is calculated to remedy immediate accidents only. By adding the favorable and unfavorable effects, we find that the latter exceed. This conclusion suggests a practical consequence. Infection being so dangerous, even when slight, not so much on its own account as by reason of its remote consequences, we must be extremely circumspect in matters of bacteriotherapy. Even when no immediate disturbance becomes manifest we may always suspect that the injection of attenuated microbes or of toxins may be the cause of some tardy lesions. This remark is applicable to bacteriotherapy procedures as well as to vaccinations. We shall again refer to this method in treating of the effects of vaccinations.

CHAPTER XIX.

MECHANISM OF IMMUNITY AND OF PREDISPOSITION.

Importance of Physical and Chemical Modifications of the Organism. Germicidal Properties of the Fluids. History. Natural Immunity. Action of the Serum of Normal Animals upon the Development, Morphology, and Virulence of Microbes. Germicidal Action of the Serum of Vaccinated Animals. Action of the Serum upon the Morphology of Microbes. Agglutinating Power. Attenuating Power of the Serum. Antitoxic Properties. Passage of Active Substances into the Secretions. Germicidal Properties of the Tissues. Modifications of the Serum in Animals Predisposed to Infections. Modifications of the Serum in the Course of Acute Diseases. Importance and Significance of Modifications in the Fluids. Nature and Origin of Different Active Substances Contained in Serums. Conclusions Regarding the Mechanism of Immunity.

The numerous researches pursued upon the interesting subject of the mechanism and predisposition of immunity have considerably elucidated certain points of this important question of general pathology. The results, however, have been so unexpected or so contradictory as to give rise to spirited controversies. The question, perhaps, appears to be more obscure than it really is, for the reason that a simple formula has been sought to explain complex facts.

Immunity is the result of multiple conditions. Therefore, exclusive theories are necessarily insufficient. Unfortunately the investigation of causes which explain the resistance to infections is surrounded by great difficulties, and the explanation of experimental results is but seldom satisfactory.

Everyone is acquainted with the famous experiment of Pasteur, who subjected a chicken to cold by plunging it into water. The chicken, which was until then refractory to anthrax, became susceptible to the disease. The conclusion that the chicken has an organic temperature too high to favor the development of the *bacillus anthracis* seems evident. When this temperature is lowered immunity is abolished. The same explanation holds good with an inverse experiment. A frog is immune from anthrax infection because its temperature is too low. When this animal is heated, as was done by Gibier, it contracts the infection. These experiments appear to be very simple and easy of explanation. In reality, however, the facts are highly complex. When we modify the

organic temperature of an animal we create a whole series of disturbances. We change the chemical state of the fluids and tissues; we completely transform the sensibility of the nervous system, the activity of the circulation, respiration, and nutritive exchanges. We thus cause an incalculable number of modifications, and do not know which play the most important rôle in the final result. The fact that the pigeon, the temperature of which is about the same as that of the chicken, quite easily contracts anthrax infection, proves that the high temperature of the chicken is not the cause of its immunity. On the other hand, the resistance of the frog does not depend upon its low temperature, since, at least during summer, the bacillus anthracis readily develops at the surrounding temperature, and the toad, the temperature of which is near that of the frog, does not enjoy the same immunity. Finally, we have made the following experiments which seem to us conclusive: Frogs were placed in an incubator for two days. They were then immersed in cold water and inoculated with anthrax. Several of them succumbed to the infection, although their temperature had fallen to its normal degree. It is, therefore, certain that by varying the surrounding temperature we act upon the entire organism; we modify its sensitiveness to living microbes and toxins, just as we modify, under similar conditions, its sensitiveness and its resistance to vegetable alkaloids. In the latter instance there is no question of favoring or hindering the development of the pathogenic agent. The result evidently depends upon dynamic modifications of the organism.

The cause of resistance and of predisposition must, therefore, be sought for in the changes presented by living beings. Numerous experiments pursued in recent years have shed light upon these modifications of the organism. According to some authorities immunity is due to a chemical state of the fluids and tissues—a chemical state hindering the development of bacteria, disturbing their functions, diminishing their virulence, and neutralizing their toxins. This is the germicidal or antitoxic theory. According to others, immunity depends upon a dynamic state of the cells which are supposedly capable of destroying the microbes. This is the vital theory, the phagocytic theory. These theories have long been and are still being discussed. I have always contended that no exclusive opinion should be held regarding these questions.

Predisposition and immunity are complex properties; they are due

to multiple factors, some of which are just becoming known. It is evident from facts hitherto observed that immunity as well as predisposition cannot be explained by an exclusive doctrine. In other words, it seems to me useless to oppose these two great theories to each other. It is better to endeavor to harmonize them and to elucidate the relations existing between them. I hope to succeed in showing that the fluids play an important rôle by weakening the pathogenic germs and by diminishing their resistance. They thus favor phagocytosis. On the other hand, the fluids being products of the cells, all modifications in the organic fluids require a previous modification in the figurate elements. Here is a new point of contact between the so-called humoral and cellular doctrines which, at first sight, appear so much at variance.

Action of Fluids upon Bacteria.

History. If a certain amount of a culture is injected into the veins of an animal and then blood drawn several times from the animal, and microbes looked for, it is seen that the number of microbes rapidly diminishes. At the end of a few hours the blood becomes sterile. The microbes accumulate in the organs in which they vegetate and from which they again invade the blood during the last moments of life. This interesting result, pointed out by Fodor[1] and by Wyssokowitsch,[2] was confirmed by a great number of experimenters, and at present seems to be indisputable. By what mechanism does the blood free itself of the parasites introduced into the circulation? In a thesis written under the inspiration of Prof. Schmidt and defended in Dorpat in 1884, Grohmann established that the blood modifies the vitality of microbes sown in it. The anthrax bacillus particularly becomes thus attenuated to the point of being incapable of killing a rabbit. The question was taken up by Fodor. By introducing the bacillus anthracis into the blood drawn from a rabbit immediately after it was killed, this author found that the number of the bacteria progressively diminished. Subsequently, after a variable lapse of time, a few microbes which had escaped the destructive action of the blood, finally got the upper

[1] Fodor. Die Fähigkeit des Blutes Bacterien zu vernichten. Deutsche med. Wochenschrift, 1887.

[2] Wyssokowitsch. Ueber das Schicksal der in's Blut injicirten Mikroörganismen. Zeitschrift f. Hygiene, 1887.

hand and succeeded in developing. The works of Flügge[1] and his disciples, Nuttal and Nissen, however, drew attention to this highly important question. Their researches showed that various microbes when sown in the blood undergo therein at first a degeneration clearly appreciable by microscopic examination. A great many of the bacteria are destroyed, while others persist and may again vegetate at the end of a variable period of time.

The researches above cited, notwithstanding their undoubted interest, are open to some objections. It was remarked that the resistance of an animal is not always related to the germicidal power of its blood. Thus, Nuttal noted that the blood of the rabbit exerted upon the anthrax bacillus a more marked destructive action than did the blood of the dog. There is yet a graver criticism to be made. The blood employed for the cultures contained figurate elements; hence it was possible that the destruction of the microbes was partly accomplished by the blood cells. Although the majority of the degenerated bacteria were found outside the leucocytes, it might, nevertheless, be supposed that the modification was due to some soluble substance derived from these elements. By heating the blood between 122° and 131° F. (50° and 55° C.), we see that it loses its germicidal action, a fact which may be due to the death of the figurate elements as well as to chemical modification. A very ingenious experiment of Petruschky, however, seemed to demonstrate that the germicidal action of the fluids is real. By introducing beneath the skin of frogs virulent bacteria, and by protecting them against the phagocytes by means of a parchment membrane, this author found that the microbes were attenuated and destroyed. There is, therefore, no escape from admitting the action of the interstitial fluids which alone had been able to diffuse. The experiments, however, which dissipated all doubt are due to Behring[2] and Buchner. These authors operated not only with total blood, but also with serum, namely, with a fluid deprived of cells, and demonstrated that this fluid possesses notable germicidal properties. Buchner further recognized that these properties diminish or disappear when the serum is heated for an hour at a temperature of 131° F. (55° C.), or when its nutritive power is increased by the addition of

[1] Flügge. Studien über Abschwächung virulenter Bacterien und die erworbene Immunität. Zeitschrift f. Hygiene, 1888.

[2] Behring. Ueber die Ursache des Immunität von Ratten gegen Milzbrand. Centralblatt f. klinische Medicin, 1888.

peptones, or by submitting the total blood to a series of congelations and meltings, operations which destroy the red blood corpuscles and liberate their contents.

Stimulated by these works, a great number of experimenters took up the study of the germicidal power of normal blood. It will suffice to cite the names of Fodor, Buchner, Behring, Karlinski, Stern, Hankin, Ogata, Jasuhara, Sanarelli, Phisalix, Gioxa, and Guarnieri. While, however, numerous facts demonstrated that under normal conditions the serum possesses germicidal properties, are the latter increased in vaccinated animals? The majority of authors who first attempted to solve this question answered negatively. They took ground on the fact that microbes develop in bouillon prepared with the tissues of refractory animals. While, on the one hand, Schottelius noticed that the bacillus of swine erysipelas vegetates with difficulty in culture media prepared with the muscles of animals which have died of this affection, on the other hand, Bitter reached an entirely different result. In all cases, however, the tissues were submitted to some alteration, and we know at present that heating destroys the germicidal properties of albuminoid substances.

In order to realize a conclusive experiment, it was necessary to study comparatively the development of microbes in the fluids of normal and of vaccinated animals. A first endeavor in this direction is that of Metchnikoff,[1] who found that the anthrax bacillus was attenuated in the blood of vaccinated sheep; but he experimented with total blood, that is, blood containing figurate elements, and he attributed the effect which he observed to the action of the latter. Sometime later, Gamaleia showed that during the anthrax fever and the fourteen days following it the aqueous humor is modified. If the anthrax bacillus is sown therein the microbe develops under a new form and loses part of its virulence. According to this author, however, this germicidal state is transitory; it disappears while immunity persists.

We then took up the study of the question and cultivated comparatively microbes on the serum of non-vaccinated animals and of animals vaccinated either against the bacillus pyocyaneus,[2] or the

[1] Metchnikoff. Sur l'atténuation des bactéridies charbonneuses. Annales de l'Institut Pasteur, 1887.

[2] Charrin et Roger. Note sur le développement des microbes pathogènes dans le sérum des animaux vaccinés. Société de biologie, 1889.

bacillus of symptomatic anthrax.[1] In both instances we observed that, as a result of vaccination, the serum became a bad culture medium for the microbe against which the animal was protected. These results were soon afterward confirmed by Behring and Nissen.[2]

The serum of vaccinated animals acts, however, not only upon the numerical development of microbes, but is capable also of modifying the forms of bacteria which resist and finally succeed in multiplying. It exerts upon them an agglutinating action, modifies their functions, and finally, as I have demonstrated with regard to the streptococcus,[3] it diminishes their virulence. All these influences are unfavorable to the microbe and may be united, as was proposed by Bouchard, under the general name of germicidal properties. The expression is not taken in its strict etymologic sense;[4] it may only be opposed to that of antitoxic property, which is applied to the discovery of Behring and Kitasato.[5] As is known, these authors demonstrated that the organism secretes antitoxins capable of suppressing or neutralizing the action of toxins. The antitoxic power, whether exercised upon the toxin, by destroying it, or, what is more likely, upon the economy by increasing its resistance, completes the germicidal power in the defense of the organism.

Here, therefore, are a series of facts showing that vaccination produces in the organism a number of chemical modifications which must play an important rôle in its resistance. But a new question has been raised by the study of morbid predispositions. Are the germicidal properties of the fluids diminished in an animal in which the resistance to the virus is diminished? The experiments which we have pursued upon this subject and those published by Bakunin and Boccardi, Bastin, and Montuori enable us to answer in the affirmative. Thus, it may be stated that the germicidal properties of the blood vary with the receptivity of the animals. They increase

[1] Roger. Nouvelles recherches sur les propriétés microbicides du sérum. Ibid., 1890. Contribution a l'étude expérimentale du charbon symptomatique. Revue de médecine, 1891.

[2] Behring and Nissen. Ueber bakterienfiendliche Eigenschaften verschiedener Blutserumarten. Ein Beitrag zur Immunitätsfrage. Zeitschrift f. Hygiene, 1890.

[3] Roger. Modification du sérum à la suite de l'érysipèle. Société de biologie, 1890. Rôle du sérum dans l'atténuation des virus. Revue générale des sciences, 1891. Le pouvoir atténuant du sérum. La presse médicale, March 4, 1896.

[4] [Antimicrobic would be a more comprehensive expression than germicidal. Translater.]

[5] Behring and Kitasato. Ueber das Zustandekommen der Diphterie-Immunität und der Tetanus-Immunität. Deutsche med. Wochenschrift, 1890.

when the resistance of the animals is strengthened, and *vice versa*. This clearly shows the interest of the present study.

Natural Immunity. If the germicidal properties of the organic fluids play a real rôle in the mechanism of immunity they must be the more marked the more resistant the animal. Authors who have studied natural immunity have at times observed results contrary to what would logically be anticipated. Nuttal, for example, noticed that the serum of the rabbit exerts a more marked destructive action upon the anthrax bacillus than does the serum of the dog. Here is an absolutely misleading fact. Is it not known that the dog, although liable to contract anthrax infection, is more resistant than the rabbit? The experiment just noted was of too great consequence to be left uncontrolled. We, therefore, took up the question and found the fact to be perfectly exact. This strange fact is true not only of anthrax, but also of symptomatic anthrax. The rabbit is naturally immune from this infection, and the guinea-pig is very sensitive to it; and yet the serum of the guinea-pig is far more germicidal than that of the rabbit. Experimentation has demonstrated this fact, and the conclusions which may be deduced therefrom deserve to be discussed.

Action of Serum upon the Morphology of Microbes. It does not suffice to study the numerical development of microbes. It is also necessary to investigate what becomes of their properties and establish whether their development is effected according to the normal type. It has already been stated that the morphology of the bacillus anthracis varies with the serum in which it develops. In the guinea-pig we find delicate regularly segmented filaments as in bouillon. In the rabbit we find rods either isolated or united in pairs. In the frog, long chains appear which are very slender and segmented at variable intervals. These first facts, which were confirmed and completed by Pane, Pernisse, and Alessi, demonstrated that the development of the anthrax bacillus does not take place in a normal manner. But it was of greater importance to determine the variations of virulence under these different conditions.

Action of Serum upon Virulence. Ogata and Jasuhara have contended that the anthrax bacillus when sown in the blood or the serum of the frog, dog, or white rat loses its virulence. If, after two or three days, it is inoculated into a mouse the animal resists. The antiseptic power of the blood of the frog is so marked that one drop suffices to confer immunity upon a mouse. The blood of the dog

and of the white rat act similarly, provided it is employed in a larger dose. The blood of a calf, which is a non-refractory animal, remains without effect. Sanarelli, experimenting with the serum of frogs freed of the leucocytes, likewise noticed that the bacillus was attenuated in this medium within three or four days if it was sporulated, and more rapidly if it was asporogenic.

Unfortunately, all these results have been contradicted. Enderlen, Petermann, and Roudenko experimented with the blood of dogs or frogs and obtained no attenuation. The action of the serum is well demonstrated only in the case of the white rat. The question seems to be one of noxious effects exerted upon the microbe itself, since the researches of Metchnikoff and Roux appear to show that it is necessary to place the serum and spores in contact in order to annihilate the pathogenic action of the latter.

On the other hand, it is not sufficient to study the chemism of the blood. The action of the organs must also be investigated. As the microbes retire from the blood current into the viscera and tissues, in order again to invade the blood at the end of life, we must study the modifications which these microbes undergo in the depths of the economy. Few researches have been pursued in this direction, and those that have been undertaken with another end by Phisalix, for example, tend precisely to demonstrate that microbes find in certain tissues favorable conditions which enable them to resist the germicidal action of the blood. This result accounts for the apparent contraction between the high germicidal power of the fluids and the absence of natural immunity. Moreover, in discussing these researches, the fact that the organism is not an inert medium seems hardly ever to have been considered. In fact, the organism reacts from the very start of the infection, at the same time that it is subjected to the action of microbic toxins. Hence, two orders of modifications take place. Some are due to the action of the microbes, and probably reduce the means of defense; others depend upon organic reactions and strengthen these means of defense.

In conclusion we would like to say that, in order to investigate in a useful manner the problem of natural immunity, we should penetrate as completely as possible the mechanism of infection and keep constantly in mind that the various modes of defense have only a relative and not an absolute value.

Acquired Immunity.

Germicidal Action of the Serum of Vaccinated Animals. As has already been stated, after the results of Nuttal, which were not perfectly demonstrative, we undertook the study of the modifications in the serum of vaccinated animals. Our first investigations, pursued with Dr. Charrin,[1] were made upon the bacillus pyocyaneus. Blood taken from normal and from vaccinated animals was kept for twenty-four hours, when the serum was separated and put in tubes, 3 cubic centimetres in each. A very small dose, 0.02 c.c. or 0.002 c. c. of pyocyaneus culture, prepared in bouillon, was then introduced into the tubes, which were shaken and subjected to study. Some experimenters thought that the germicidal action of the serum under these conditions depended simply upon the fact that the culture made in bouillon was transferred to a different medium—*i. e.*, the serum. We therefore often took our virus from cultures made in normal liquid serum. The results were identical in both instances. In fact, on the following day it was possible to clearly see with the naked eye notable differences in the mode and intensity of vegetation of the microbe, according as the culture was made in normal serum or in serum obtained from vaccinated animals. The normal serum was completely opaque, turbid, and of a bluish-green color. It contained a few flocculi which increased in number on the following days. On the other hand, the serum of the vaccinated animals became but very slightly turbid. The bacilli were united in small masses floating in the fluid. On the following days the development was more noticeable, and the differences, although appreciable, were less striking.

When, however, the animal is well vaccinated, the cultures made in its serum always preserve a peculiar appearance. The fluid remains clear, and the microbes are united in small masses which are scattered when the tube is shaken. Moreover, while the bacillus gives a fine blue color in normal serum, it produces no pigment in the serum obtained from vaccinated animals; the culture medium assumes a dirty brown hue.

These first results led the author to study other infections from this point of view, and he experimented with the bacillus of symptomatic

[1] Charrin and Roger. Note sur le développement des microbes pathogènes dans le sérum des animaux vaccinés. Soc. de biologie, 1889.

anthrax.[1] Guinea-pigs were either vaccinated with the virus attenuated according to the method of Arloing, Cornevin, and Thomas, or inoculated with small amounts of virulent fluid beneath the skin of the ear. Four or five days after the last preventive inoculation, in order to ascertain their resistance, a few drops of symptomatic anthrax serous exudate mixed with lactic acid were injected into the animals. Those guinea-pigs which resisted were bled after a period varying from eight to twenty-two days after the test inoculation, and their serum was inoculated comparatively with the serum of normal guinea-pigs. The smaller amounts inoculated the more marked were the differences in development. Thus, when 0.08 c.c. to 0.1 c.c. of symptomatic anthrax serous exudate were mixed with 3 c.c. of serum, it was noticed on the following day that growth had begun in all the tubes, but was less pronounced in the serum obtained from the vaccinated animals. On the second day the differences were far more appreciable. Even the macroscopic appearance showed that development was far more luxuriant in the normal serum, which was completely opaque, and microscopic examination revealed therein a far greater number of bacilli.

A short time after our first investigations the contributions of Behring, Nissen, and Zasslein appeared, which contributed additional facts to those observed by us. Behring and Nissen established that vaccination of the guinea-pig against Metchnikoff's vibrio imparts to the serum of this animal a germicidal power which is absent in the normal state.

Action of the Serum upon Morphology. The modifications presented in the morphology of the bacillus anthracis have already been referred to in connection with normal serum. The influence of the serum of vaccinated animals is still more definite. Let us take, for example, the cultures of the bacillus pyocyaneus. The microbes developing in normal serum present nothing special. They are small rods analogous to those observed in artificial culture media habitually employed in bacteriology. The appearance is altogether different in the serum of refractory animals. In the latter instance the microbes are united in chains of variable length made up of six to ten segments. The length of these strepto-bacilli is less than that of the normal bacilli. The size of the segments varies; some of

[1] Roger. Nouvelles recherches sur les propriétés microbioides du serum. Société de biologie, 1890. Contribution à l'étude expérimentale du charbon symptomatique. Revue de médecine, 1891.

them are extremely short, being half as large as a normal bacillus; many attain, and a few exceed, the normal length. In general, all the segments of the same chain are nearly of the same dimensions. Some diplo-bacilli and a few isolated ones are also observed. The protoplasm of these elements does not stain as well as in the normal state, and not infrequently some clear patches are found. Finally, these elements manifest a remarkable inclination to form groups, and, instead of swimming freely like normal bacilli, they are found in small masses, which accounts for the clotted appearance of the cultures. The differences observed with symptomatic anthrax are no less marked from this point of view.

Agglutinating Power of Serum. Cultures made in the blood of vaccinated animals present a peculiar appearance due to the delay of development or to modifications imposed upon certain functions. At the same time, however, an agglomeration of the figurate elements may be observed, which imparts to the culture medium a clotted appearance which is altogether characteristic. In studying with Dr. Charrin the development of the bacillus pyocyaneus in the serum of vaccinated rabbits we first observed the agglutinating power of serums. We noted that the microbes, often united in chains, manifested a strong tendency to form groups, and, instead of freely swimming like normal bacilli, they formed small masses. This fact explains the appearance of the cultures. In fact, these remain clear and transparent; the microbes fall to the bottom of the tube, where they unite in clots.[1] Dr. Metchnikoff[2] made similar observations with the avicide vibrio, then with the microbe of pneumonia; but he later recognized that this agglutinating property does not belong to the sera of all vaccinated animals. It is lacking, for instance, in animals immunized against the bacillus of hog cholera. Gruber[3] took up the question and completely modified the method. He introduced a new and very simple procedure for determining whether or not a given serum was derived from a vaccinated animal. He took a small amount of culture and mixed it with serum upon a slide. When the serum was derived from a normal animal the microbes remained disseminated; when it was obtained from a vaccinated

[1] Charrin and Roger. Note sur le développement des microbes pathogènes dans le sérum des animaux vaccinés. Soc. de biologie, Nov. 23, 1889.

[2] Metchnikoff. Etudes sur l'immunité (4th memoire). Annales de l'Institut Pasteur, 1891, pp. 473, 474. Etudes sur l'immunité (5th memoire). Ibid., 1892, p. 294.

[3] Gruber. Theorie der aktiven und passiven Immunität gegen Cholera, Typhus, und Verwandte Krankheitprozesse. Munchener med. Wochenschrift, 1896, p. 206.

animal the microbes agglomerated and agglutinated. Gruber observed this result with the microbes of cholera and typhoid fever and noticed that the phenomenon is clearer the more intensely the animal is immunized. From this time on innumerable contributions appeared upon the question of agglutination. The chief results obtained may be given in résumé in the following conclusions:

The agglutinating power often exists in the serum of normal animals. Horse serum agglutinates the cholera vibrio, the colon bacillus, and the typhoid bacillus. Likewise the sera of most animals agglutinate the bacilli introduced by the first inoculation of anthrax, independently of any relationship between the intensity of agglutination and the immunity of the animal. Thus, according to Gengou, the serum of the rat agglutinates in a dilution of 1:10, the serum of the guinea-pig in 1:20, that of the dog in 1:100, and that of man in 1:500. Man is far more sensitive to anthrax than the rat, and yet his serum is fifty times more active. The serum of the guinea-pig and that of the dog have an almost equal agglutinating power, while the resistance of these animals is quite different.

The agglutinating power appears not only in vaccinated animals, but also in the course of infections, and this property, which is acquired also by the blood, has been turned to profit by Widal for diagnostic purposes. As a rule, the better the individual resists a disease the earlier the agglutinating power appears and the more energetic is its action. The serum prognosis of P. Courmont is based upon this fact.

The serum acquires agglutinating properties not only with respect to bacteria, but also as regards more highly organized plants, as we have shown to be the case, for instance, with the fungus of aphtha (Figs. 11 and 12, pp. 311, 312). Finally, cellular elements, such as red blood corpuscles, and organic substances, such as casein, may be agglutinated as well as microbes. Animals which have received blood drawn from various species yield a serum agglutinating the red blood corpuscles of the blood which has been injected into them. The result is identical when milk is employed.

The agglutinating reaction is specific. It is exercised only upon the element against which the animal reacts. This fact may serve to differentiate microbic species and even simple varieties.

Attenuating Power of Serum. We have already stated that certain streptococci develop as readily in the serum of normal as in

that of vaccinated animals. In pursuing our researches we recognized that the numerical development was the same, while the pathogenic properties were quite different. Take, for instance, two cultures twenty-four hours old, one prepared in normal serum, the other in that of a vaccinated animal. If the same amount of each of these cultures is injected beneath the skin of the ear of two rabbits, the results are found to be quite different. In some instances the culture prepared in normal serum proves highly virulent, and if a large dose, say sixteen drops, is introduced, the animal dies within two or three days. The local lesion is slight; a general infection takes place, as may be proved by cultivation from the viscera. The cultures prepared in the serum of the vaccinated animal, under the same conditions as in the preceding, give rise to a local lesion, a more or less extensive erysipelas; but the general state remains good and the animal rapidly recovers.

The streptococci thus acquire different properties according as they are developed in the serum of normal or of vaccinated animals. In both instances vegetation is similar, but the microbes derived from the serum of the vaccinated animal lose much of their virulence and become attenuated. This is an important fact from the standpoint of general pathology.

It is to be noted, however, that the agents which develop in the serum of animals rendered refractory do not lose all of their pathogenic power: there is a reduction but not abolition of virulence. This is not to be wondered at, since vaccinated animals develop a local lesion when active microbes are inoculated into them.

These remarks are applicable also to the pneumococcus, which likewise becomes attenuated in the serum of refractory animals.[1] This result was confirmed by Arkharow.[2] The researches of this author were strongly criticised by Metchnikoff, in whose laboratory the investigations were pursued. Therefore, we shall not dwell upon them. We must mention, however, a very curious fact discovered by Mosny. According to this experimenter the pneumococcus lives longer in the serum of a vaccinated than in that of a normal rabbit. This fact has nothing paradoxical about it. Dr. Mosny himself remarks that the microbe is, so to speak, in a state of latent life in

[1] Roger. Rôle du sérum dans l'atténuation des virus. Revue générale des sciences, June 30, 1891.

[2] Arkharow. Guérison de l'infection pneumonique chez les lapins. Archives de médecine expér., July, 1892.

the serum of the vaccinated animal. While the microbe does not die, it does not develop. It behaves as in an unfavorable medium. It does not secrete the substances which arrest its own vegetation.

The attenuating action of serum was further demonstrated by the experiments of Dr. Courmont. This scientist cultivated the staphylococcus aureus in comparative series in the sera of vaccinated and of normal animals. After several successive passages in the two media he transferred the microbes to bouillon, and these last cultures he employed for inoculation. In this manner he avoided introducing therapeutic serum. The virulence was preserved intact in the normal serum, while it was reduced or destroyed in the sera obtained from animals which had been rendered refractory.[1] Analogous researches pursued by Nicolas[2] proved this conclusion to be applicable to the bacillus of diphtheria. We might also cite the experiments of Denys and Leclef with streptococci and those of Babes, Sternberg, Béclère, Chambon, and Ménard, demonstrating that the virus of hydrophobia and that of vaccinia lose their properties in contact with the sera of refractory animals.

Antitoxic Properties of Serums. As microbes act mostly by the toxic substances which they secrete, it was natural to investigate the action of serum upon microbic products. We owe to Behring and Kitasato the first experiments upon this question, experiments which oppened a new route for therapeutics. These facts are at present too well known to require long discussion in this place. The serum of an animal vaccinated against diphtheria has but very slight germicidal power (Nicolas), but it possesses the far more important property of neutralizing the diphtheritic toxin. The antitoxic power of the serum is so marked that a guinea-pig weighing 400 grams is preserved against a fatal dose of toxin by 0.008 c.c. of serum. In other words, 1 c.c. of serum preserves 50,000 grams of living matter. Such is the strength of the serum furnished by the Pasteur Institute.

Tetanus is comparable to diphtheria in that the microbe remains localized at one point of the organism and acts only by its toxins. Its mode of attack and the mode of defense of the economy are similar to what occurs in diphtheria. The serum of animals vaccin-

[1] Courmont. Sur les propriétés bactéricides ou microbiophiles du sérum du lapin, suivant que cet animale est vaccine contre le staphylocoque pyogène ou prédisposé à cette infection. Archives de physiologie, January, 1895.

[2] Nicolas. Pouvoir bactèricide du sérum antidiphtérique. Thèse de Lyon, 1895.

ated against tetanus is also an antitoxic serum. Behring and Kitasato, to whom also this discovery is due, affirm that this serum, when injected into animals, preserves them from tetanus, and may even cure the established disease. They assert that it is possible to save a mouse which already manifests the characteristic contractures. These experiments, however, repeated by Tizzoni and Cattani, Vaillard, and again by Kitasato himself, gave negative results from a therapeutic standpoint. Soon after Roux and Vaillard[1] showed that the serum injected before inoculation preserves the animals. When introduced simultaneously with the toxins, or a little after, it diminishes the intensity of the symptoms and permits the development of only a local tetanus. It is absolutely ineffectual when injected into animals already presenting contractures.

In a great number of infections it may, perhaps, be possible to prepare, by certain experimental contrivances, either germicidal or antitoxic sera. To this end the methods of vaccination may be varied. This has been accomplished by researches pursued with regard to cholera and typhoid fever. Pfeiffer obtained a germicidal serum against the vibrio of cholera. The animals which furnished this fluid received vibrios killed by means of chloroform fumes and heat and increasing doses of living vibrios. The serum acted against the disease produced by intraperitoneal inoculation of cholera bacilli, but it failed when it was tried upon animals inoculated through the intestine. Even in cases of peritonitis the serum acts only when it is injected a short time after inoculation and when the dose of virus introduced is not too large. Pfeiffer, who has made a thorough study of this question, has shown that the serum should be injected half an hour after inoculation in order to succeed. It is inert if it is employed after an hour and a half. The same author established that $\frac{1}{10}$ of a milligram of serum suffices to neutralize 2 milligrams of culture, but he recognized that even a considerable amount of serum does not protect against intraperitoneal injection if the dose of the culture is greater than one platinum loopful per 100 grams of weight of animal. The fact is that when the culture is introduced at the end of a certain time or in too large amount, not only the microbes introduced, but also the toxins elaborated within the organism or contained in the culture must be taken into account. The serum is only germicidal, it weakens and kills the figurate

[1] Roux and Vaillard. Contribution a l'étude du tétanos. Annales de l'Institut Pasteur, February, 1893, p. 65.

elements; it is not antitoxic, namely, it exerts no action upon the poison of cholera. As a matter of fact, Pfeiffer, Wassermann and Metchnikoff have noted that vaccinated animals which are refractory to virulent inoculation are as sensitive to the influence of toxins as normal animals, or even more sensitive.

These results explain why Pfeiffer's methods do not succeed much with man. In the case of spontaneous disease the question is one of intoxication rather than of infection. The microbe multiplies in the intestine, but it is the toxins absorbed therefrom which act, and it is precisely these toxins that are uninfluenced by the serum. Cholera is, therefore, altogether comparable to diphtheria and tetanus. In all three cases the microbes multiply at a certain point in the organism, and all the symptoms depend upon the absorption of their toxins. Hence, it was natural to apply to cholera the fundamental principles which guided Behring in the study of diphtheria. This is what was undertaken by Ransom, one of the disciples of Behring, and by Drs. Roux, Metchnikoff and Taurelli-Salimbeni. These authors extracted from cholera cultures a very active soluble poison against which immunity may be conferred by operating progressivelv. A serum is thus obtained which proves active against choleraic intoxication and meets clinical requirements. It is thus possible to prepare two serums against cholera: one acting upon the living element, the other upon the toxin. The latter is efficacious against experimental cholera, which may be produced in young rabbits by causing them to swallow choleraic cultures. In this, as in the case of man, the process is one of vibrionic intoxication. In the investigations of Metchnikoff, Roux, and Taurelli-Salimbeni, 56 per cent. of the animals experimented upon survived, and 16 per cent. of the controls. In the same order may be mentioned Funck's researches demonstrating that the poison contained in the protoplasm of the typhoid bacillus gives rise to the appearance of germicidal substances in animals. The serum is very efficacious against infection by the living microbes, but exerts no influence upon the typhoid toxins. Chantemesse, on the other hand, by utilizing a special toxin, prepared an antitoxic serum.

It would seem at first sight that nothing is easier of explanation than the mode of action of antitoxic serums. The idea suggesting itself immediately—and such was Behring's idea—is to assume that the antitoxin neutralizes the toxin as an acid neutralizes a base. The serum is supposed to contain a true antidote destroying the

poison. Hence the name *toxinicide*, which is sometimes given to it. Behring's conception was combated by Buchner, Ehrlich, Roux, Vaillard, Calmette, Bouchard, etc. If a quantity A of serum neutralizes a quantity B of toxin in such a manner as to render the mixture inoffensive, 2A should neutralize 2B, 3A should neutralize 3B, and so on. Such is not the case, however. When the quantities of serum and of toxin are increased progressively a moment arrives when the toxin acts. Any amount of serum may then be employed, but there will no longer be any antitoxic effect. Thus, an inoffensive mixture in the dose of 1 cubic centimetre will prove fatal if 2 or 3 cubic centimetres are injected. We hardly need dwell upon this fact which, from a practical standpoint, is of great consequence, since it explains certain failures of serum therapy. It is also important from a theoretical standpoint, since it proves that the process is not one of neutralization in the chemical sense of the term. Another objection was formulated by Buchner. This author prepared a mixture of tetanus toxin and antitetanic serum. He injected it into a mouse without giving rise to any symptoms; but he discovered that the mixture was still active as regards the guinea-pig.

When inoffensive doses of the mixture of toxin and serum are introduced the animal may be rendered sensitive to the neutralized poison by modifying its resistance by means of certain microbes. Thus Roux and Vaillard showed that guinea-pigs vaccinated against the vibrio of Massouah take tetanus when they are injected with a mixture of toxin and serum, which mixture is inoffensive for normal guinea-pigs. On the other hand, a normal guinea-pig was inoculated with the same mixture. No symptom was produced, but when, a few days later, the soluble products or various microbes such as the Kiel bacillus or colon bacillus was injected, tetanus was declared. The poison was, therefore, always present. A modification of the organism sufficed to enable it to act.

Calmette obtained analogous results by means of venoms. He prepared a mixture of venom and serum, and noted that this mixture was inoffensive. He heated it for five minutes at 154.5° F. (68° C.). At this temperature the action of the serum was destroyed, while that of the venom remained intact. He then injected the mixture, which was inactive a little while before, and this time the animal died. There was, therefore, no destruction of poison, but simply a simultaneous presence in the fluid of two substances with antagonistic action.

The conclusion is evident: Since the antitoxin does not act upon the toxin, it therefore influences the organism itself in such a manner as to enable the cells to resist the action of the poison or, perhaps, not to be penetrated by it at all.

Passage of Active Substances into the Secretions, and Notably into the Milk. The active substances which are found in the blood of vaccinated animals possess the property of passing into certain secretions, natural fluids, and transudations. This was demonstrated by Stern,[1] Prudden,[2] and Gottstein[3] by studying the serous fluid of vesicatories, of ascites, pleurisy, hydrocele, and the amniotic fluid. Unlike the microbic toxins, which are rapidly eliminated by the urine, as was shown by Prof. Bouchard, the active substances of the serum do not seem to pass into the urine. When an animal is vaccinated its urine possesses no therapeutic property. Such may not be the case when therapeutic serums are injected, since an observation reported by Vagedes shows that tetanus antitoxin passes into the renal secretion. It is detected therein for eleven days. It is difficult, however, to draw a conclusion from this case, since it was that of a patient afflicted with tetanus, and it is not known what rôle is to be attributed to infection and what to serum therapy.

The only secretion which is important from a practical standpoint is the milk. Since Brieger and Ehrlich[4] called attention to this fact a great number of experimenters have recognized that the milk contains therapeutic substances, but in quite small amounts. Ehrlich showed the immunizing power of milk of animals vaccinated against abrin and ricin. Klemperer and Levy established the same fact as regards the typhoid bacillus; but the milk of an immunized goat was ten times less active than the serum of the same animal. Particular researches in this connection have been pursued with regard to cholera and diphtheria. The works of Popoff, Ketscher, and Klemperer demonstrated the passage of anticholerine into milk. Popoff[5] showed that the active principle is found in the serum of

[1] Stern. Ueber die Wirkung des menschlichen Blutes und anderer Körpersflüssigkeiten auf patogene Mikroörganismen. Zeitschrift f. klin. Medicin, 1890, Bd. xviii.

[2] Prudden. On the Germicidal Action of Blood Serum and Other Blood Fluids. Medical Record, 1890.

[3] Gottstein. Zusammenf. Uebersicht über die bakterienvernichtende Eigenschaft des Blutserum. Therap. Monatshefte, 1891.

[4] Brieger and Ehrlich. Ueber die Uebertragung von Immunität durch Milch. Deut. med. Wochenschrift, 1892.

[5] Popoff. Uebertragung der Immunität gegen Cholera mittels der Milch einer vac-

the milk and was destroyed by boiling. Ketscher showed that the milk acts when it is injected beneath the skin. When it is introduced by the alimentary canal it is inert. The experiments were made upon vibrionic peritonitis, and, therefore, it was the germicidal substance that passed into the milk. In order to study the antitoxic substance, we must consider the researches pursued with diphtheria.

Wassermann and Ehrlich[1] employed goats' milk. At the beginning of vaccination 5 c.c. were required to neutralize the toxin. Later, 0.1 c.c. sufficed. The serum was twenty times more active. The authors remark, however, that a goat yields in one month a litre and a half (a quart and a half) of serum, or 30 litres of milk. It would, therefore, be advantageous to employ the latter secretion if it could be concentrated so as to obtain the active substance in a small volume. This is what Wassermann tried to do. After coagulating the milk by means of lab-ferment, he precipitated the active substance by sulphate of ammonia. The precipitate, dried *in vacuo* and again dissolved, proved highly effective; 0.125 c.c. of the fluid thus obtained sufficed to neutralize 0.9 c.c. of the diphtheritic poison.

The employment of milk may, therefore, be of service in therapeutics. The same is true of eggs. In fact, Klemperer's researches show that anticholerine is found in the yelk of the egg of hens vaccinated against the vibrio. According to Sclavo, the white of the egg contains the diphtheritic antitoxin. Here, therefore, is a new field open to therapeutics. It is not impossible that some day, when active substances will be prepared in a state of purity, milk and eggs of vaccinated animals will replace the serum.

Germicidal Properties of Tissues. Do the tissues, under the influence of vaccination, undergo modifications analogous to those of the fluids? Such is the question which we endeavored to elucidate after our first investigations on the germicidal properties of serum. The problem was not new. It had long been laid down and taken up by various experimenters, and almost always received a negative answer. The majority of experimenters admit, as a dogma, that microbes develop equally well in all tissues deprived of life, no matter

cinierten Kuh. Vratch, 1893, No. 10 (Anal. Centralblatt f. Bakt., 1895, Bd. xvii., p. 166).

[1] Wassermann. Ueber Konzentrierung der Diptherie-Antitoxine aus der Milch immunisierte Thiere. Zeitschrift f. Hygiene, Bd. xvii. p. 233. Ehrlich and Wassermann. Ueber die Gewinnung der Diptherie-Antitoxine aus Blutserum und Milch immunisierte Thiere. Ibid., p. 239.

whether they are derived from animals enjoying natural or acquired immunity, or not. Unfortunately, the contributions thus far published are open to criticism. Bouillon prepared with the muscles of animals has always been employed. It is to be noted that heat destroys the germicidal properties of the fluids, and it must evidently act in the same manner upon the tissues. Hence, it was necessary to practice cultivation without any previous preparation. The experiment thus conceived was not as simple as might seem at first sight. The majority of aërobic microbes do not develop in the interior of dead tissues where oxygen is lacking. It is difficult, if not impossible, to appreciate with accuracy the intensity of vegetation inside an organ or a tissue and to recognize whether or not development is similar in animals sensitive to the disease and in those that are naturally or artificially immune.

All these difficulties disappear when an anaërobic agent is employed, which lives free from air, and the multiplication of which may be appreciated with some accuracy by the amount of gas liberated. These various conditions are fulfilled by the bacillus of symptomatic anthrax. Hence, we have chosen this microbe for studying the problem laid before us. We first investigated the behavior of this bacillus when inoculated into tissues separated from the body and derived from normal, viz., non-vaccinated animals.

We operated in the following manner: The animal, rabbit, or guinea-pig being killed by hemorrhage, we detached, with every antiseptic precaution, the four extremities. Then, by means of a Pravaz syringe, we injected into each limb from 1 to 5 drops of the serous fluid drawn from an anthrax tumor of a guinea-pig. We thus made four injections with one animal. Immediately after the virus was injected the four extremities were placed in sterilized vessels and put in an incubator with a temperature of 93.2° F. (34° C.). At the end of fifteen or seventeen hours it may readily be recognized by palpation that the tissues of the rabbit as well as those of the guinea-pig are infiltrated with gas. This emphysema is really due to the development of symptomatic anthrax and not to putrefaction, since it is not produced in non-infected limbs prepared in the same manner. We are therefore led to conclude that the tissues of the rabbit and guinea-pig present, after death, excellent culture media for the bacillus of symptomatic anthrax. There is no relation between the natural immunity of the animals and the resistance which their tissues, deprived of life, may oppose to the multipli-

cation of the microbe. This result may be compared to that observed in serum. It seems, however, less paradoxical, since the muscles of the guinea-pig are invaded as readily by the microbic agent as those of the rabbit. It is no less interesting to note that, after death, the tissues of a naturally immune animal no longer opposes the development of a pathogenic agent which could not develop during life.

Let us now consider what occurs in vaccinated guinea-pigs and in rabbits the natural immunity of which has been reinforced by means of preventive inoculations. The animals were treated in the same manner as in the preceding experiments: the four limbs were separated from the body and inoculated at the same time and in the same manner as the limbs of normal animals. At the end of fifteen hours the tissues of the latter are infiltrated with gas; those of the vaccinated animals do not contain any. Sometime later it is found that emphysema develops in the vaccinated limbs. Crepitation is appreciable at the end of twenty-four or twenty-eight hours; but the amount of gas is very small and in nowise comparable to that infiltrating the tissues of the normal limbs. After thirty-six or forty hours the differences are still quite notable. Although the tissues of the vaccinated limbs give the sensation of emphysema, it is easy to see that the tissues of the normal animals are so swollen that even a slight touch will reveal the characteristic crepitation.

In some of our experiments we took the precaution to irrigate the circulatory system in order to remove all trace of blood before practising inoculation. For this purpose, the animal having been killed by hemorrhage, we first detached one of the thighs. After ligating the vessels opened during this operation, we incised the abdominal wall and injected through a canula introduced into the aorta a 7:1000 sterilized salt solution, which came out through the inferior vena cava. The amount of fluid thus employed was 360 c.c. The remaining thigh, which had been thus washed, was then detached, and the two limbs were inoculated in the same manner and placed in the incubator. We found that the washing of the circulatory system did not modify the results. It neither restricted nor favored the development of symptomatic anthrax and in nowise modified the differences which are observed according as the tissues experimented upon were those of normal or of vaccinated animals.

The procedure employed in these researches is open to some

criticism. It serves to elucidate only one of the phenomena accompanying microbic development. It may be objected that the bacilli develop in the tissues of vaccinated animals and that only one of their functions is suppressed. Such an objection is not in harmony with the facts known of the biology of anaërobics; at any rate, the objection is of little value. In fact, it matters little whether the vegetation or the function of the microbe is checked. It suffices for us to establish that development differs according as the tissues employed are those of vaccinated or of normal animals. This result, which seems to be undeniable, proves that a chemical modification takes place, no matter whether this modification occurs in the muscles, the connective tissue, or the interstitial fluids. The only legitimate conclusion to be drawn from our investigations—and this is precisely the answer to the question which we proposed to solve—is that the bacillus of symptomatic anthrax develops with difficulty in the tissues of vaccinated animals.

This conclusion is in harmony with that arrived at by Bitter, who found that extracts of tissues possess germicidal properties. Donissen also learned that the extract of the tissues of rabbits vaccinated against the pneumococcus possesses vaccinating properties.

A very skilful experiment of Voswinkel tends to prove that the tissues of certain naturally refractory animals are likewise germicidal. This author experimented upon frogs the blood of which he replaced by sterilized salt water. He then injected into them 1 c.c. or 2 c.c. of anthrax culture. The microbes introduced soon perished, while those which were kept at the same temperature in salt water preserved their vitality. On studying the phenomena more closely, Voswinkel recognized that while some bacilli were incorporated by some remaining leucocytes, the majority disintegrated outside them.

Modifications of the Serum in Animals Predisposed to Infections. After studying the chemical modifications occurring in the organism when its resistance is increased we were naturally led to investigate what happened under opposite conditions. As is known, a great number of procedures may be employed to increase the sensitiveness of animals to infection. This may be realized, for example, by injecting into them the soluble products of streptococci, viz., cultures filtered through a porcelain bougie and not heated. The animals thus treated, when later inoculated, die more rapidly than normal animals. Under these conditions the serum is far less germicidal

than under normal conditions. At times the differences are so marked that fifteen or twenty hours after inoculation of the sera microscopic examination shows innumerable germs in the cultures prepared with the serum of the weakened animals, while in those cultures made with normal serum only one or two chains are seen in each microscopic field. The differences disappear soon after, and, at the end of two or three days, the two cultures are numerically similar, but not equally virulent. Animals which receive the culture derived from the sera of predisposed animals die before those which receive a culture developed in normal serum.

The results which we obtained with the serum of predisposed animals thus represent the counterpart of those furnished by the study of the sera of vaccinated animals. In the latter case the microbe is attenuated; while in the former instance it is exalted, or rather it seems to be exalted; for some experiments, which are yet incomplete, tend to show that the sera of predisposed animals act, not upon the microbe, but upon the inoculated animal whose resistance it reduces.

The streptococcus is not the only microbe that secretes predisposing substances. Like substances are secreted by the staphylococcus. In this case also the serum, as was shown by Courmont, loses its germicidal properties. To use the author's expression, it becomes bacteriophilic.

Analogous modifications are observed under various circumstances. At times diminution of resistance seems to depend upon a diminution of the alkalinity of the blood. This hypothesis explains how overexertion weakens the resistance of the white rat to anthrax infection. In fact it is known that the resistance of this animal depends upon the high alkalinity of its blood. The analyses of Drouin demonstrated that this alkalinity diminishes in rats when they are forced to do violent muscular work. Likewise, according to Zagari and Innocenti, the alkalinity of the blood is weakened in animals subjected to the action of chloral, tartaric acid, and alcohol, and in heated frogs, and in pigeons subjected to fasting. In all cases there is a remarkable parallelism between the diminution in the alkalinity of the blood and the reduction of resistance. The influence of fasting was particularly demonstrated by the experiments of Canalis and Morpurgo.[1] After four or six days of fasting the pigeon lost

[1] Canalis and Morpurgo. Intorno all' influenza del digiuno sulla disposizione alle-malattie infettive. Roma, 1890.

its immunity against anthrax. At this time it possessed very little, if any, germicidal power. In only one experiment the blood remained germicidal, and this time the animal preserved its immunity. Gaertner[1] likewise observed that the staphylococcus vegetates more luxuriantly in the blood of rabbits whose resistance to infection was reduced by means of deficient alimentation and repeated bleeding. On the other hand, if bleeding is only once practised, the resistance is not diminished, even when the loss of blood is great. In accordance with this result, the blood remains germicidal, as was shown by Bakunin and Boccardi.[2]

Modifications of the Serum in the Course of Acute Diseases. It might be assumed that the germicidal properties of the serum increase when the individual recovers, and that they diminish when the patient dies. In reality the phenomena are far more complex. Even in fatal cases the organism generally reacts. Therefore, the germicidal properties may increase. From the very start of our researches we noted with astonishment that the serum of animals succumbing to an infection is at times as strongly germicidal as the serum of vaccinated animals and likewise hinders certain functions. The animal dies because the protective substances are insufficient in quantity or have appeared too late. They may nevertheless exert a harmful action upon the microbes that have invaded the organism. Hence, cultures obtained from individuals dead of certain infections may be destitute of virulence. This occurs constantly in cases of streptococcic infections. The organism succeeds in attenuating the microbe, but the latter has time to secrete toxins which injure the principal organs and render recovery impossible. Hence, it is not rare to see death occur after destruction of microbes. We therefore remark that in the course of infections two different processes go on simultaneously. Microbic products are elaborated which tend to diminish the germicidal properties, while the reactions of the organism tend to increase them. We may readily conceive the variability of results according as one or the other process predominates.

In certain instances the rôle of reduction of germicidal power in the course of infections has been appreciated. By producing local

[1] Gaertner. Beiträg zur Aufklärung des Wesens des sog. Praedisposition. Ziegler's Beiträge zur patholog. Anat., 1890.

[2] Bakunin and Boccardi. Ricerche su la proprieta battericida del sangue in diversi stati dell' organismo. La Riforma medica, 1891, t. iii. p. 445.

lesions, which subsequently became generalized, Bastin found that invasion of the organism is preceded by a diminution of the germicidal power. The degree of this diminution is in direct ratio to the intensity of the infection. On the other hand, in two women suffering from local abscesses, Bastin found that as regards the staphylococcus the blood was more germicidal than normal, and this fact accounted for the localization of the lesion. Analogous to these results are those obtained by Kiouka, Szekely and Szana, Kruse, and Pansini. Experimenting with the staphylococcus, bacillus anthracis, and pneumococcus, these authors noticed that the germicidal power diminished and disappeared when infection became generalized—*i. e.*, when the microbes passed in large numbers into the blood. On the contrary, in typhoid cases the germicidal properties persist until death and the microbes do not invade the blood (Kiouka).

Importance and Significance of Modifications in Fluids. In view of the facts reported, it may be concluded that there is a remarkable parallelism between the variation of the organic resistance and the action of the blood upon bacteria. When the resistance is increased the protective rôle of the blood is more marked, and *vice versa*. These correlations are at times so perfect that, as regards the pneumococcus, for example, the serum culture gives the measure of receptivity (Kruse and Pansini). The results are not comparable, however, unless the experiment is pursued upon the same animal species.

These facts have not, however, sufficed to convince all scientists. Some objections have been raised against the so-called humoral theory which we must briefly consider. We shall not dwell upon erroneous criticisms. It is quite certain, for example, that germicidal power does not depend upon a change of medium—*i. e.*, upon transference from bouillon to serum. On the contrary, the germicidal action is unmodified when a germ grown in the serum of a normal animal is inoculated into the serum obtained from a vaccinated one.

The important objection is the argument that the germicidal properties do not exist in the blood circulating in the bloodvessels. They appear when the blood is in an abnormal condition, when it has been coagulated or defibrinated. This is, so to speak, an artificial property developing after death, due, perhaps, to disintegration of leucocytes and to diffusion of substances contained in them.

It may be replied, in the first place, that it is quite strange that the germicidal, attenuating, or antitoxic power of the serum varies with the degree of resistance, that it is increased when the animals are vaccinated, and diminished when their immunity is weakened. In this manner the blood of vaccinated animals acquires a new power which is in a latent state in the organism, and becomes manifest as soon as this fluid leaves the vessels. This power would thus act when it is useless. A good many facts, however, tend to prove that the protective action is real and is readily exercised during life. The passage of active substances into natural effusions, such as the serous fluid produced by vesicatories, ascites, pleuritic, hydrocele, and the amniotic fluids and their presence in milk, cannot be explained otherwise than by the admission that the blood contains a diffusible soluble principle.

Moreover, there are a few experiments which prove, by other methods, that the protective action really exists during life. This may be demonstrated by protecting the microbes against the phagocytes by means of parchment bags, by injecting germs beneath the skin, and after a few minutes studying the modifications presented by them. De Giaxa and Guarnieri introduced the microbe into a segment of artery tied at the two ends. The modifications were found to be the same as outside the organism. Drs. Denys and Leclef injected streptococci beneath the skin of the ear of normal and of vaccinated rabbits. In the former they noted that the microbes rapidly developed and that the leucocytes were not late in appearing at the spot; but, while some of these fulfilled their phagocytic action, the majority remained passive and did not attack the invaders. In the vaccinated animal, on the contrary, the microbes rapidly disappeared. The number of leucocytes making their appearance at the spot was the same as in the former instance, but the microbes were weakened by the serum, and the leucocytes succeeded in devouring them within a few hours. These original and accurate experiments elucidate the various phases of the struggle between the microbe and the organism. Whether the animal is vaccinated or not, the leucocytes migrate with the same facility; but this afflux of cells is not necessarily followed by phagocytosis. The microbes are more readily picked up because they had been previously affected by the fluids—*i. e.*, by the chemical substances dissolved in the blood serum. Another conclusion to be drawn from these researches is that the active substance in the serum of vaccinated animals can

no longer be considered as a *stimulin*, exciting the phagocytic power of the cells. It seems rather that the serum acts upon the microbe by weakening its vitality or by neutralizing the noxious substances secreted by it.

Nature and Origin of the Various Active Substances Contained in the Serum. We have indicated the principal modifications presented by the blood in the course or in consequence of infections. We must now consider the relationship existing between the various substances the effects of which have been alluded to. We must ask what is the significance and the cause of germicidal, agglutinating, and antitoxic actions.

It may first be stated that certain normal animals furnish agglutinating serums, others germicidal serums. Vaccination does not, therefore, produce a new property. On the contrary, it increases or modifies an already existing property. The study of serums obtained from normal and vaccinated animals demonstrates, on the other hand, that there is no constant relationship between the agglutinating and germicidal powers. Thus, the serum of the normal dog agglutinates the bacilli introduced by first inoculation of anthrax, but it does not destroy them. Moreover, numerous observations demonstrate that the agglutinated microbes are not dead and that, under certain conditions, they are capable of development. The two properties may be separated. Heating to 131° F. (55° C.) abolishes the germicidal power, but modifies the agglutinating power very little, if at all. The two substances may also be separated by dialysis. The germicidal substances pass through the collodion sac; the agglutinating substances do not.

By investigating the relationship existing between the germicidal and the therapeutic powers of serums, Fränkel and Sobernheim found that serum heated to 140° F. (60° C.) loses its germicidal action, but preserves its preventive power. It still confers immunity upon guinea-pigs into which it is injected. Bordet took up the experiment and demonstrated that, by adding a certain amount of normal serum to the heated preventive serum, the germicidal power reappeared. This highly interesting result shows that the serum of a vaccinated animal acts by means of two substances. One is a specific substance resisting a temperature of 141° F. (60° C.); the other, present in normal serum, is a common substance which is incapable of destroying bacteria except when the latter have been influenced by the specific substance. In other words, vaccination

causes the appearance of a substance which renders the microbe sensitive to the alexin contained in every serum.

Continuing the study of these facts, Bordet demonstrated that this specific substance unites with the pathogenic agent against which the animal is immunized. Under its influence the microbes lose their motility and, in the second phase, they agglutinate. After the remarkable contributions of Bordet, agglutination must be considered a physical phenomenon comparable to coagulation. It results from a change in the relations of molecular adhesion between the bodies of the cells and the fluid containing them. In order for this agglutination to be produced it is necessary for the substance to possess a certain mineral composition, and, notably, contain sodium chloride. When the agglutinating serum is placed in contact with microbes suspended in distilled water the latter remain separate; when sodium chloride is added they come together and agglutinate. These results are observed not only outside but also within the organism. Fränkel and Sobernheim injected into guinea-pigs the serum of a vaccinated animal after heating the serum to 158° F. (70° C.). They, therefore, introduced a non-germicidal serum. The serum of the animal thus treated acquired the germicidal power which had disappeared from the injected serum. This fact is important, since it demonstrates that we must not, as is often done, believe the properties of the serum to be absolutely unlike those of the plasma. Furthermore, recent researches by Rehm, Camus, and Pagniez seem to demonstrate that the alexins are not artificial products and that they pre-exist in the circulating blood.

The origin of the specific substance is completely unknown. All that is known about it is that it is not produced or contained in the leucocytes.

The investigations of Deutsch demonstrated that the liver, kidneys, and suprarenal capsules contain very little agglutinin. The spleen, the lymphatic glands, and the bone-marrow contain more, but the amount is still less than that found in the blood. On the other hand, the lungs contain more of it, but these organs also contain it normally. It would be interesting to learn whether the lungs play an important rôle in the formation of this substance. As to the alexins, the researches of Denys, Havet, and Hahn have conclusively shown that they proceed from the leucocytes. But there is another problem connected with this subject. Do the white blood corpuscles alone elaborate alexin? Cannot other cells also participate

in this function? Even supposing that the leucocytes are the sole producers of the germicidal substance, is it to be presumed that they retain it in their interior and that it serves only to destroy the microbes ingested by the leucocytes? When it is encountered in various fluids, is it to be supposed, following Metchnikoff's school, that alexin diffuses only after the destruction of leucocytes? Or is it to be admitted, as does Buchner, that it is constantly given off as a secretion? This is the only point upon which the adherents of the so-called humoral and cellular doctrines of immunity are not agreed. The question is undoubtedly of great importance from a theoretical standpoint. If the germicidal substances remain enclosed within the leucocytes, phagocytosis retains its importance. If they diffuse, the phenomena of extracellular digestion become predominant and the modifications of the humors assume an important position. It is well to remark, moreover, that even supposing that the germicidal substances do not leave the leucocytes—and this hypothesis seems to us contradicted by certain facts above reported, since the sensibilizing substance is not of leucocytic origin—the modification of the fluids explains all acquired immunity. The phagocyte is capable of digesting only those microbes which have been acted upon by the specific substance, viz., that substance which is found in fluids modified by infection. Thus, owing to the fine contributions of Bordet, we return to the conception of acquired immunity as it was understood years ago by Bouchard and his disciples.

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CHAPTER XX.

CONGENITAL INFECTIONS AND HEREDITY.

Passage of Microbes through the Placenta. The Law of Brauell-Davaine. Experiments upon Anthrax Infection. Transmissibility of Some Human Infections. Congenital Variola. Peculiar Characters of This Clinical Form. Course of Temperature in Congenital Variola. Its Analogy with Experimental Variola. Transmission of Chronic Infections: Leprosy, Syphilis, and Tuberculosis. Congenital Dystrophies of Infectious Origin: Rôle of Syphilis and of Tuberculosis. Transmission of Immunity. Laws of Colles and of Profeta. Rôle of Father and of Mother in the Transmission of Immunity. Conclusions.

The history of heredity of infectious diseases[1] must be considered from a triple standpoint: transmission of the living microbe from parents to progeny; transmission of modifications in fluids and cells, namely, chemical or dynamic changes occurring in the organism of the parents in the course or in consequence of infections; influence of diseases of the parents upon the development of the child during and after intrauterine life.

Passage of Microbes through the Placenta.

Let us first consider the simplest question: the contamination of the fetus by living germs. Clinical observation has long demonstrated the reality of fetal infections; it will suffice to cite variola and syphilis. There are, however, other infections in which the problem is more complex and more difficult of solution. The explanation of inherited tuberculosis has given rise to numerous contradictory works upon the subject. Some writers have asserted the possibility of fetal contamination by the father or by the mother; others, pursuing the discussion on similar lines to those which apply to syphilis, have described cases of early or of tardy heredity, while still a third school has totally rejected the idea of direct transmission and held tubercular heredity to be nothing more than a congenital predisposition to contract the disease. According to the last-mentioned hypothesis, it is not the bacillus but the soil favorable to its development that is transmitted.

[1] Roger. L'hérédité dans les maladies infectieuses. Gazette hebdomadaire, October 11, 18, and 25, 1889.

Experimental pathology has taken up the problem, and the number of works bearing upon this question is very considerable. From a general point of view, we may first cite the magnificent researches upon diseases of the silkworm. It is known that these worms are liable to two main infections: pebrin and flacherie. Pebrin is transmitted from generation to generation through the eggs which contain the pathogenic agent. The latter is incorporated with the egg inside the female chrysalid, and becomes an integral part of the embryo and the worm evolved from it. The male does not transmit the disease, but it may exercise upon the progeny a harmful influence as expressed by weakness of the worm and the inferior quality of its cocoon. In the case of flacherie the agent of the disease resides in the intestine and does not invade the eggs. The worms issuing from contaminated animals do not have the disease, but they are weak and almost certainly predestined to become victims of the contagion. It is the morbid predisposition that is transmitted. Do we not find in the history of these affections of the silkworm the counterpart of what occurs in syphilitic and tuberculous infections of more highly developed organisms?

Intraplacental Transmission of Anthrax. It was with anthrax, the experimental disease par excellence, that the first attempt was made to solve the problem whether or not infectious germs may pass through the placenta and invade the fetus. Brauell, in 1858, reported four experiments upon a colt and three sheep. Microscopic examination showed no bacilli in the fetus, and inoculation into animals gave rise to no symptoms. Davaine added one, and Bollinger, in 1876, reported three more negative results. The question then seemed to be settled and the law of Brauell-Davaine, that the placenta was a perfect filter, was admitted. A first opposition was raised by Arloing, Cornevin, and Thomas, who were convinced that symptomatic anthrax was transmitted from the mother to the fetus. In 1882 Straus and Chamberland published a few facts which seemed to confirm Brauell's law; but, by pursuing their studies, these authors later recognized that such transmission was at times possible. They experimented upon twenty guinea-pigs; microscopic examination of the blood, liver, and the spleen revealed no bacilli. The fetus presented no alterations whatever, and the blood did not offer the agglutinating property which is observed in animals dead from anthrax. But the result was altogether different when the authors employed another method—*i. e.*, when they resorted to cultures and intoxica-

tions. They thus obtained several positive results, especially by cultivation, since inoculations quite often failed. On examining twenty-six fetuses they detected the bacillus anthracis in fourteen of them. Their investigations established the fact that in certain rare cases anthrax is not transmitted to any of the fetuses of the same litter; in other instances the disease attacks all of the fetuses; in most cases it affects only some of them. At all events the number of bacilli penetrating the fetal organism is extremely small; this fact accounts for the negative results obtained by the first investigators. The experiments of Straus and Chamberland gave rise to a great number of researches which confirmed the conclusions of the two French scientists. Such were those of Perroncity, Koubassoff, Birch-Hirschfeld, Rosenblath, and Latis.

There are also some interesting observations as regards man. Marchand reports the case of a woman who died from anthrax a few hours after confinement, and her child succumbed to the same infection four days later. There were numerous bacilli in the placenta and ulcerations in the chorionic villi. Paltauf reports a case in which bacilli were found in the lungs of a fetus of five months from a woman suffering from anthrax. In two cases observed by Eppinger and in another by Morisani the results were negative. It may be concluded from all these experiments and from the observations thus far published that the bacillus of anthrax may pass through the placenta; but the fact is far from being constant, and the number of bacilli invading the fetus is always very limited. We now appreciate why the bacilli were not found by microscopic examination except in a few cases.

It is quite difficult to determine the frequency of intraplacental transmission of anthrax. At any rate, in this case, as in all other cases of this kind, statistics can give no more than illusive results and present no interest from a scientific standpoint. The bacillus anthracis passes into the fetus in a variable manner because the conditions which seem apparently identical are in reality dissimilar; the animals react differently, according to a multitude of circumstances which are often very difficult to explain. In other words, the experiment is modified by various conditions which favor or hinder this passage. The experimenter, therefore, instead of discussing the frequency of the phenomenon, should endeavor to learn why and especially how it is produced. We are, therefore, indebted to Dr. Malvoz, who attempted to explain the mechanism by which the intra-

placental passage of anthrax takes place. The researches of this author show that the indispensable condition resides in the existence of placental alterations. Hence, it is intelligible why non-pathogenic microbes, such as the bacillus prodigiosus, are incapable of passing the barrier. The same is true of inert substances, such as sulphate of barium and India ink; if other bodies can pass it is owing to lesions produced by solid or resisting substances. It may, therefore, be said in conclusion that no passage of figurate elements occurs without alteration in the placenta. Moreover, Malvoz remarks that the bacilli are transmitted to the fetus more easily in the guinea-pig than in the rabbit, a fact which is explained by the greater frequency of placental alterations in the former of these animals.

These very interesting experiments give no final solution of the problem; they only lead to the investigation of the conditions which favor placental alterations which, under apparently identical conditions, give rise to different lesions. The problem is undoubtedly a difficult one; but it is a satisfaction to have its terms laid down and to see how successive discoveries bring out new complications in the question.

Intraplacental Transmission of Human Infections. We have thus far considered microbes especially attacking lower animals; we now come to those which are of greater importance for human pathology.

The study of the streptococcus is extremely interesting, owing to the fact that it is the most frequent agent of puerperal septicemia. Lorrain had already observed peritonitis in children born of septic women. The observations of Simone, Lebedeff, Hanot, Luzet, Haushalter, and others demonstrate the intraplacental transmission of the streptococcus. A case observed by the author seems to demonstrate that the death of the fetus does not occur in every case. A woman suffering from measles gave birth to a child of eight months weighing four and one-quarter pounds. The author obtained a pure culture of streptococcus with the blood of the umbilical cord; the child had an attack of icterus, but it soon recovered, and a month later, when it left the ward, it weighed five and one-quarter pounds. It had not only withstood the streptococcic infection revealed by the culture, but even gained a pound in weight.

As has already been stated, the child does not seem to be infected in the course of erysipelas. In twelve cases women suffering from erysipelas were delivered at full term, and all the children survived without presenting any notable disorder.

The existence of congenital pneumonia has long been admitted. Grisolle asserts that this affection is not rare in the newborn, and that it ends fatally within a few hours, when autopsy will reveal disseminated foci and even abscesses in the lung. The last-mentioned condition renders somewhat doubtful the nature of the disease transmitted and suggests rather the idea of pyemia with pulmonary involvements. Netter, who pursued interesting researches on this subject, reported, in 1886, the transmission of the pneumococcus in guinea-pigs; of four fetuses the issue of a contaminated mother, two contained the microbe. Analogous facts have been observed by Foa and Uffreduzzi in the rabbit and Ortmann in the guinea-pig. The transmission of the pneumococcus is, therefore, possible in animals as well as in the human species. Thorner reported a case in which the mother was confined at full term after defervescence of pneumonia; the child succumbed in thirty-six hours, and the autopsy revealed hepatization of the lower left lobe, and the microscopic examination detected the pneumococcus. The most complete observation is Netter's. In this case the child succumbed after five days. This lapse of time might lead to the suspicion that perhaps a contamination had taken place after birth. However that may be, the lesions were very marked, consisting in hepatization of the right apex with pleuritic and pericardial pseudomembranes and fibrinopurulent exudates in the meninges. This was, therefore, a case of infectious pneumonia the nature of which was demonstrated by bacteriological examination; the generalization of the lesion is readily accounted for by the direct entrance of the morbid germs into the blood. Bacteriological investigations may likewise detect the pneumococcus in fetuses from mothers suffering from any one of the various affections which may be produced by this microbe. Netter cites an observation of Hecker concerning a woman who died of a suppurative meningitis; the child, delivered by a Cesarean operation, died at the end of thirty-four hours, and the autopsy showed left lobar pneumonia with pleuritic and pericardial effusions. The author had the opportunity to observe a pregnant woman suffering from measles and intense bronchitis. She gave birth to a child of eight months which succumbed a few hours after birth. Pure cultures of pneumococcus were obtained from the blood and organs of the fetus, and the same microbe was found in large numbers in the expectorations of the mother. Here is an example of an infection which, in spite of its benign character and its apparently exclusive location in the bronchi, had really

infected the maternal organism, since the pathogenic agent had invaded the fetus and caused its death. Friedländer's microbe also may, according to Netter, be transmitted to the fetus. On the other hand, Foa and Rattone believe that it favors abortion, but does not pass to the placenta. In pregnant guinea-pigs inoculated through the peritoneum, abortion occurred within thirty-six or forty-eight hours, and no microbes were found either in the fetus or in the placenta.

While speaking of human diseases we may mention typhoid fever, since the transmission of this infection to the fetus seems to be well demonstrated by recent observations. Eberth's bacillus, penetrating directly into the blood, kills the fetus by inducing septicemia. This is a new illustration of symptomatic variations which may be observed according to the age of the subjects or the mode of entrance of the virus.

With reference to cholera, we may cite an observation of Tizzoni and Cattani upon a woman suffering from this infection who gave birth to a fetus of five months. In this case, as in the majority of other diseases, microscopic examination did not detect the presence of any microbe, while cultivation enabled the experimenters to find the comma bacillus.

Recurrent fever has also been known to be transmitted to the fetus, and in this instance Spitz was able to discover Obermeier's spirilla in the embryo. It must also be remembered that the transmission of intermittent fever to the fetus seems to have been established by some of the older observers. Stokes recorded the case of a pregnant woman suffering from tertian paroxysms whose child had convulsions on the days when the mother enjoyed apyrexia. Pitres and Aubanais have seen malarial mothers giving birth to children which presented hypertrophy of the spleen and febrile paroxysms on the same days and hours as their mothers. Schurig, Hoffman, and Russel have published similar observations. Among the infectious diseases the pathogenic agents of which are unknown or little known we may cite acute articular rheumatism (Follack and Schaeffer) and especially hydrophobia, which are sometimes transmitted to the fetus.

The transmission of the hydrophobic virus was first demonstrated by clinical observation. Lafosse saw a rabid cow give birth to a calf which presented the first symptoms of hydrophobia three days after birth. Perroncito and Carita have recently studied this ques-

tion from an experimental standpoint: A rabbit which had been inoculated with hydrophobia gave birth to a litter of four. One day prior to the appearance of paralytic symptoms the spinal cord of two of the young ones was inoculated into two guinea-pigs, one of which developed hydrophobia, the other resisted. The transmission of the virus of hydrophobia, however, seems to occur but exceptionally. Moreover, it is known that the blood has nearly always been found free from infecting properties, and, on the other hand, it is well established that only those microbes that can invade the blood are capable of penetrating the placenta. Several experiments were made in the Pasteur Institute with negative results. The medulla of eight of the young born of hydrophobic animals were inoculated, and none of these medullas proved virulent. It may, of course, be objected that perhaps in the fetus the virus does not reside in the nervous centres. This objection is refuted by Zagarri's experiments. This author operated upon fourteen pregnant females inoculated with the fixed virus; thirty-two young ones were thus obtained for the experiments. The nervous centres, liver, sometimes the entire fetus were used, but the inoculations practised upon rabbits and guinea-pigs produced no results.

Transmission of Eruptive Fevers.

Vogel, Heine, Rilliet and Barthez published several cases of congenital measles, the mother having been attacked before confinement. We know also of a few cases of congenital scarlatina recorded by more or less ancient authors—Baillou, Ferrario, Portier, and others. Such facts must be very rare, since the author has never observed a case of congenital measles or scarlatina.

Congenital Variola. Variola is the disease which has furnished the greatest number of observations of congenital infection. The facts observed are the more valuable, as the child on coming into the world sometimes presents characteristic lesions and there can, therefore, be no doubt as to the nature of the disease. A few cases possess the certainty of an experiment and have served purposes of inoculation with positive results (Gervis, Jenner). Hereditary variola is particularly frequent when the mother contracts the disease toward the end of gestation. As in the case of anthrax, in twin births the contamination of only one of the infants is a possible event. In the observation of Kaltenbach, a woman suffering from variola was delivered of three children; two of them had pustules, the third

did not. Not infrequently the variola of the fetus is more recent than that of the mother; the latter may be convalescent and give birth to a child bearing fully developed pustules. In a few cases the fetus has contracted the disease while the mother remained exempt. Finally, even when there is no transmission, properly so called, and the fetus presents no alteration, its organism may have been profoundly modified under the influence of the maternal disease, and thus it is born vaccinated, having acquired immunity in the uterus.

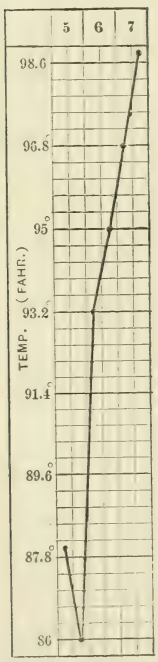
Such are the results admitted by all classical authorities. My observations are not in harmony with the descriptions thus far given. During the epidemic of 1901, eighteen women were confined in our hospital. The children never presented at birth the slightest eruption. One of them manifested no disturbance whatever, and flourished. The others appeared at first to be exempt, but a more attentive observation revealed a certain number of disorders, showing that, notwithstanding the absence of easily appreciable symptoms, these children were all variolized.[1] The germ of variola had constantly passed through the placenta. Infection was produced whether the maternal variola was discrete and curable, as was the case in six of them, or fatal, as occurred in the other patients. The passage of the germs is rapidly effected. One of the children was born a day before the mother was taken sick; another a few hours after invasion; three others a day after. In eleven cases confinement occurred on the second or the third day of the disease, that is, a little before the eruption or coincidently with it, and once eight days after. Three children were born at seven months, the others at full term. At first they seemed to be normal, and nothing would have suggested a congenital infection if their temperatures had not been taken. The information thus obtained was unexpected. All these children were hypothermic; in no case did the thermometer, introduced into the rectum, rise to 98.6° F. (37° C.); in most cases it remained below 96.8° F. (36° C.). In some instances it fell rapidly to 87.8°, 86°, and even 82.4° F. (31°, 30°, and 28° C.). This hypothermia seemed to express a profound infection which had overwhelmed the organism. If the child is sufficiently resistant and capable of reacting, the temperature rises and may reach normal or even 104° F. (40° C.). In the latter case there are also observed cutaneous manifestations expressing an effort of the organism to

[1] Roger. Variole des nouveau-nés. Soc. méd. des hôpitaux, March 29, 1901.

eject the morbid element. According as these reactions appear or are absent the observations may be divided into two groups.

The first group contains six cases in which the children succumbed without presenting any symptom indicative of variola. A woman suffering from hemorrhagic variola to which she succumbed on the eighth day had, on the day prior to the invasion, given birth to a child at full term weighing six and one-half pounds. At the time when the child was admitted to our wards, that is three days after birth, it presented a rectal temperature of 96 F. (35.6 C.). It was suffering from a slight icterus, which became aggravated the following day, when the child succumbed with a temperature of 96.4° F. (35.8° C.). The second case was that of a child born at seven months. The mother had a discrete variola from which she easily recovered. The child was born on the third day of the mother's disease, the day following the eruption. Two days after birth it developed a slight icterus. Its temperature fell on the fifth day to 86° F. (30° C.). Then, as if a reaction was coming, it rose rapidly, and in two days reached 98.6° F. (37° C.), when the child died. (Fig. 40.) The other cases were analogous. Death may supervene very rapidly ; thus a child born at seven months of a mother suffering from hemorrhagic variola, to which she succumbed sixteen hours later, lived only five hours. Its rectal temperature, taken ten minutes after birth, was 87.8° F. (31° C.).

FIG. 40.



Congenital variola.

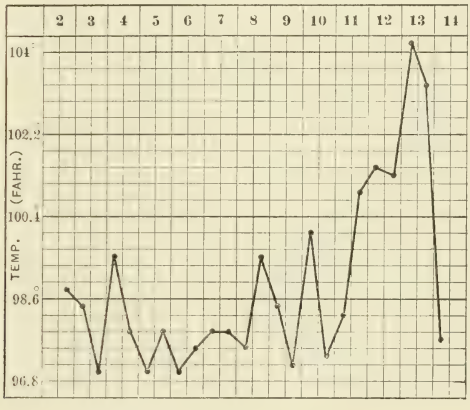
In such cases the symptomatology consists in a subnormal temperature and icterus. It may, therefore, be questioned whether we are not in the presence of weak children and whether we have any right to speak of variolar infection. The analysis of the second group of cases will enable us to answer this question. We shall first cite the case of a child born at full term. The mother developed on the day of her confinement the first symptoms of a hemorrhagic variola, to which she succumbed on the eighth day. The temperature of the child at first oscillated around 96.8° F. (36° C.); it rose on the ninth day to 100.7° F. (38.2° C.), to fall again the next day to 98.6° F. (37° C.). On that day a scarlatiniform erythema made its appearance and covered the whole body, being more marked on the

face. The child seemed to be in a satisfactory condition, but it suddenly died in syncope the following night. In the other observations the evolution was more complete; it terminated in the development of a characteristic eruption which in most cases was quite discrete, and sometimes remained at the papulous phase. This occurred in four cases.

The temperature may rise as high as in the adult. A child had 104° F. (40° C.) on the thirteenth day coincident with the appearance of a few papules on the body. Death supervened the following day.

In several cases the eruption thus remained at the stage of papules, either because the evolution was suddenly interrupted by death or because the elements were rapidly dried. Purulent transformation is possible, however. A well-developed child was born at full term;

FIG. 41.



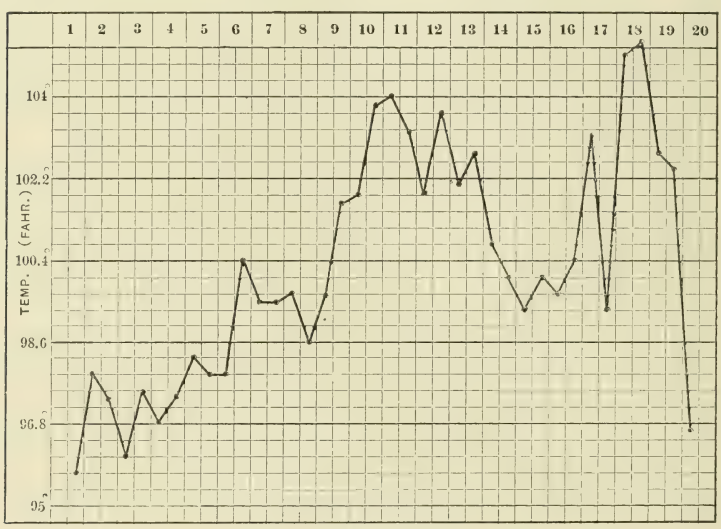
Congenital variola.

the mother had suffered for three days from hemorrhagic variola, to which she succumbed six days later. The rectal temperature of the child, which was 95° F. (35° C.), rose on the following days. At the same time icterus developed. Then a febrile movement occurred on the tenth day, during which the temperature reached 104° F. (40° C.). A crop of about fifteen papules appeared upon the back, face, and hands. The child emaciated and refused the bottle. The evolution of the eruption continued. The fever, as in the variola of the adult, fell to rise again, and its renewal coincided with a purulent transformation of the eruption. This fever of suppuration was suddenly interrupted on the twentieth day by a final hypothermia. (Fig. 42.) Here is a case in which the evolution is similar to that in the adult. It differs, however, in two important characteristics—an initial

hypothermia and discrete eruption contrasting strikingly with the gravity of the general phenomena.

Whatever may be the clinical form of the infection, the results shown by the necropsy are fairly uniform. As in the adult, there are frequently found degenerations of the liver and kidneys and small hemorrhages on the surface of the viscera, notably of the kidneys. In one case the suprarenal capsules were the seat of a diffuse hemorrhage. Histological examination reveals profounder lesions; myocarditis is very frequent and assumes the same characters as in the adult. The liver is profoundly altered, and the changes in its cells

FIG. 42.

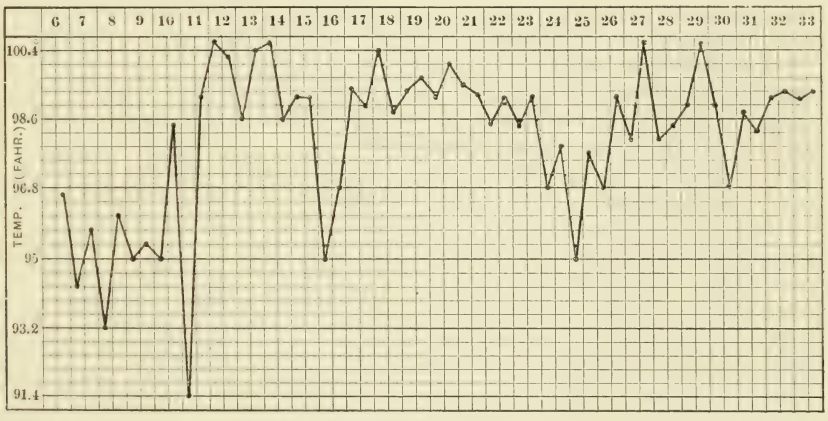


Congenital variola.

may perhaps account in part for the frequency and persistence of hypothermia. Although grave, the disease is not necessarily fatal. A child which once had a temperature as low as 91.4° F. (33° C.) recovered. This favorable evolution is probably due to the fact that the mother had been revaccinated in the seventh month of her pregnancy. Two pustules developed. This vaccination was, however, insufficient to establish complete immunity, since this woman was attacked two months later by a discrete variola from which she easily recovered. Confinement took place at full term, two days after the onset of the disease and twenty-four hours before the development of the eruption. The child, well constituted, weighed six and one-

half pounds. It was vaccinated without success the day following its birth. In spite of its fine appearance and the fact that it took nourishment satisfactorily, this child was hypothermic; its rectal temperature oscillated around 95° F. (35° C.) and even fell to 93.2° F. (34° C.). Eleven days after birth the temperature suddenly fell to 91.4° F. (33° C.). In the evening it rose to 99.2° F. (37.3° C.), and a slight erythema appeared on the skin with three papules, two on the arm and one on the neck. Three days later the papules were dry and the child seemed convalescent, but on the sixteenth day the temperature again fell to 95° F. (35° C.), to again rise. This thermal variation coincided with the appearance of a second eruption consisting of three papules situated on the scalp, the thigh, and the

Fig. 43.



Congenital variola. Recovery.

leg of the same side. Two days later two new papules were found on the arm and three upon the abdomen. The total number of eruptive elements was eleven. The general condition was serious, but the child took nourishment fairly well. The following days the papules dried, and an improvement seemed to follow, but on the twenty-fourth day a new hypothermia was observed accompanied with vomiting and diarrhea. Under the influence of subcutaneous injections of artificial serum the temperature rose and reached normal in a definitive manner on the thirty-first day. At the same time the other disturbances disappeared and the child became convalescent. This brief description showed that the variola of the newborn differs totally from that of adults. It is announced by hypothermia, which

is in some cases slight, in others very pronounced. Jaundice appears (in only one of the eleven children it was absent). Then two evolutions are possible: either the child will become weak and die in hypothermia, without presenting other symptoms, or else an eruption develops, generally coinciding with a rise in temperature. It sometimes consists in a simple rash, but more often presents small papules. The eruption recurs several times, but it is almost always very discrete. Among those who succumbed, three only had an abundant eruption. The eruption may evolve as in the adult, but this is exceptional; the papules do not suppurate, but soon dry and are covered with small crusts. Recovery is exceptional, and death supervenes from the fourteenth to the twenty-first day by gradual weakening or syncope. The profound lesions of the myocardium explain the sudden termination.

This peculiar evolution of congenital variola is of considerable theoretical interest. In fact, it recalls the description of variola in the rabbit, such as we have described it with Dr. Weil. We know by many examples that the pathology of the first period of life is often analogous to the pathology of animals. Thus, tuberculosis takes a course in young children similar to that in the small rodents utilized in laboratories. The same is perfectly true of variola: rabbits inoculated with variolar pus generally succumb without producing any eruption; when they present any it consists, as in newborn children, of a limited number of disseminated papules which become covered with crusts without suppuration. Like children, the animals become emaciated and weakened and succumb in hypothermia. It is not only because the reactionary modes are analogous in the newborn and in animals that the evolution is comparable, but also because in both cases infection is thorough and overwhelming. In animals we inject relatively large quantities of the virus; in the fetus the microbes also penetrate in large numbers, as has been proved by the examination of the amniotic fluid. The study of the blood leads to similar conclusions. From the child who died three hours after birth we took a drop of blood immediately after death. This blood, examined with the assistance of Dr. Weil, had the following formula:

Polynuclears	17.0	per cent.
Mononuclears	63.5	" "
Large mononuclears	7.5	" "
Neutrophile mononuclears	10.0	" "
Eosinophile mononuclears	1.0	" "
Eosinophiles	0.5	" "
Irritation cells	0.5	" "

There were also found a great number of nucleated red corpuscles.

Without dwelling upon theoretical considerations which the study of variola in the newborn gives rise to, the author believes that the knowledge of its peculiar evolution is of certain practical interest. The characters of the fever chart and of the eruption impart to it a particular physiognomy and assure it a separate position in the clinical forms of this infection.

Intraplacental Transmission of Chronic Infections.

It now remains to study the chronic infections, syphilis, tuberculosis, and leprosy. The heredity of syphilis has been more thoroughly investigated than that of any other disease, owing to the fact that in this malady the mode of contagion is in general easily determined, while in the case of tuberculosis interpretations are often difficult. In the case of a tubercular child the question may always be raised whether it inherited the disease or whether it was infected after birth while living with its parents. Of course, syphilis may also be contracted under the same conditions, but then the existence of a primary lesion indicates the origin of the infection and suffices to remove all doubt. Hereditary transmission of syphilis is particularly frequent when both parents are affected and the disease is recent. After two or three years infection of the fetus occurs more rarely, although it is a possible event for a long period of time. When only one of the parents is contaminated the fetus may still be infected; but maternal heredity is far more important than paternal. The father less surely transmits syphilis; the inoculations practised by Mireur have established in fact that the semen is not virulent. When the father alone is contaminated the fetus dies toward the sixth or seventh month and pregnancy is terminated by miscarriage. If, however, the child is born at full term it is often found to be free from or only slightly infected by the disease in the case of maternal syphilis. Moreover, some recent observations tend to demonstrate that syphilis may be transmitted during two generations; this is what results from the facts published by Lannelongue, Fournier, and Besnier.

In most cases the mother is infected before or during the fecundation; occasionally, however, she contracts the disease during pregnancy. What happens to the fetus? This question has been variously answered. Mandrou and Kossowitz have denied the hereditary transmission of syphilis after conception, while Cullerier is of

the opposite opinion. It seems that it may really occur, but only when the infection has been acquired before the sixth (Ricord) or the seventh month (Albernethy, Pidoux). After this epoch the fetus remains exempt, and this may readily be accounted for by the fact that at the beginning of infection syphilis remains localized at the point of inoculation, and does not pass the limits of the lymphatic system.

The manifestations of hereditary syphilis have been divided by Fournier into two groups according as there is transmission of the virus or parasyphilitic symptoms appear. In the former instance the manifestations are similar to those in the adult; the difference consists only in the absence of the initial lesion, which fact is due to the direct infection of the blood. This mode of penetration of the pathogenic agent likewise explains the great rapidity of the evolution and the consequent confusion of the phenomena which it is still customary to divide into secondary and tertiary. We hardly need recall that syphilitic accidents may appear at very different periods of life; sometimes clinically appreciable manifestations exist at the time of birth; more frequently they appear toward the sixth week; at times they appear tardily at the age of thirteen or even fifteen or twenty years of age. Parasyphilitic manifestations shall be studied later in connection with nutritional disturbances which may occur in other infections.

The history of syphilis likewise furnishes the solution of several problems which, from the standpoint of general pathology, are of great interest. Although it is the mother who commonly transmits the disease to her product, there are incontestable cases in which it has been inherited from the father, the mother remaining absolutely sound. Even in such a case, however, the maternal organism is modified. The woman who gives birth to a syphilitic child may suckle it with impunity, since she is in no danger of contagion. How is this fact to be interpreted? Is the maternal organism impregnated by products secreted by the microbe of syphilis? Or is it a case of slight syphilis remaining latent, perhaps localized in the uterus, as has been argued by Fränkel?

What has been demonstrated as true of syphilis is less evident with regard to tuberculosis. There is one fact which seems to be well demonstrated, viz., that individuals of tubercular parentage are often attacked by tuberculosis at a more or less advanced stage. This idea is very old, for Hippocrates admitted the heredity of

phthisis. Recent statistics give a more precise idea of the transmission of the disease in families. The statistics of Brehmer in the sanitarium of Gorbersdorf and those of Detweiler in Falkenstein present identical results, 36 per cent. in the former's statistics, which were based upon 13,000 patients; 35 per cent. in the latter's, which involved a study of 6000 cases. Hereditary tuberculosis may become manifest at any age; but, contrary to what was once believed, it is not rare during early childhood. We owe to Dr. Landouzy our knowledge of the fact that the victims of tuberculosis during the first two years of life are very numerous. While the fact is incontestable, its interpretation is difficult. We find ourselves in the presence of two diametrically opposite theories. As has already been stated, some believe that the bacillus is transmitted, others that it is the soil. On the one hand it is asked how it is possible for the father to transmit tuberculosis to the fetus without contaminating the mother, and how may inherited tuberculosis remain latent for years and become manifest at an advanced age. On the other hand, the example of syphilis is cited to explain these facts: the occurrences are similar in both cases, and why should we not admit for tuberculosis what is true with regard to syphilis? Such is the reasoning. Let us now consider the results of clinical observation and experimentation.

There are some observations on record in which children succumbed so rapidly that it is hardly possible to presume a contagion after birth. But these facts may leave some doubt in the mind, since it must be admitted that, in a child predisposed by heredity, acquired tuberculosis may run a rapid course and prove fatal in a few weeks. This would be an evolution similar to that which is observed in animals inoculated in laboratories. The same thing may not be said of those cases in which tubercular lesions were found in stillborn fetuses. Some such facts have been observed in the human species. The first observations are due to Ollendorf, Peter, S. Charrin, and Berti, and belonged to an epoch when Koch's bacillus was yet unknown. More important is the observation of Sabouraud: a child born of a mother suffering from acute miliary tuberculosis succumbed eleven days after birth. At the necropsy the liver and spleen were found full of tubercular granulations in which the presence of the characteristic bacillus was detected. In an observation reported by Armanni the liver and spleen of a fetus issued of a tubercular mother were inoculated into guinea-pigs and gave tuberculosis to these ani-

mals. In a case reported by Bar and Renon the blood of the umbilical cord contained Koch's bacillus.

Intraplacental transmissibility is, therefore, incontestable; it is, however, much less frequent in the human species than in animals, especially in the bovine species. Dr. Chauveau has found tubercles several times in fetuses of consumptive cows. By inquiring of 1165 Danish veterinarians, Bang found that 32 of them had observed tubercles in newborn calves. While most of these cases may be regarded as doubtful, since no mention is made of the presence of Koch's bacillus, such criticism cannot be addressed to the observations of Johne, De Malvoz, and Brouwier. In fetuses from tubercular cows these authors not only found tubercles but bacilli as well. Misselwitz and Bang have reported similar facts.

To complete the data of observation it was necessary to resort to experimentation. The results obtained seem to be somewhat contradictory. To the positive findings of Landouzy and Martin are opposed negative results of other experimenters. On the other hand, De Renzi, who experimented upon eighteen pregnant guinea-pigs, found tubercles in the fetus five times. In order that there may be contamination, the inoculation must be practised at least thirty-four days before the birth of the young. In several cases these perished in marasmus without becoming tuberculous. Whatever the final solution may be, the results obtained in guinea-pigs should not be applied to man, as there is no proof that the same is true of man. For, by inoculating the white mouse, Gärtner found that the tubercle bacillus passed to the fetus, and the same experimenter saw the bacilli infecting the eggs of tubercular canary birds, while the result was negative in hens.

A last question is whether a tubercular father may beget a tubercular child; in other words whether the semen may be the vehicle for the bacilli. As to this point there seems to be no doubt. Even when the genital organs seem to be sound the semen of a tubercular subject may contain the bacilli, as has been demonstrated by the researches of Landouzy and Martin, Weigert, Jani, Bozzolo, and Niepce. Can, however, the bacillus infect the ovum? Baumgarten, who is one of the most ardent advocates of the heredity of tuberculosis, does not hesitate to answer in the affirmative. In one case, having artificially fecundated a rabbit with the semen of a tubercular rabbit, he detected the bacillus in the ovum. This curious observation does not lead to a firm conclusion, since it is not known

what would become of this bacillus or of the ovum—the bacillus might not proliferate or the ovum might be killed by the microbe, and thus not be developed. It is true that Baumgarten believes that the tissues of the fetus and of the newborn oppose a considerable resistance to the infectious agent, and, to explain tardy hereditary tuberculosis, he contends that the bacilli may long sojourn in the lymphatic glands and the bone-marrow without causing any disturbance. Later, under the influence of some occasional cause—an inflammation or a traumatism—the tissues lose in some degree their vitality and are attacked by the microbes. This conception is supported by the researches of Landouzy and Martin and by the more recent investigations of Birch-Hirschfeld and Schmorl. These authors demonstrated that in fetuses of tubercular mothers the apparently sound organs sometimes contain the specific bacillus. Maffucci's experiments may also be adduced in support of tardy inherited tuberculosis. This author, by inoculating various microbes into the eggs of hens, noticed that infection did not become manifest until some time after the eggs were hatched.

When a fetus of a mammalian is born with tubercular lesions the latter present some interesting peculiarities. Congenital differs from acquired tuberculosis, not in the anatomical characters of the tubercles, but in their localization. The liver is the organ most frequently and seriously involved, owing to the fact that the bacilli conveyed through the umbilical vein first colonize in the liver.

In brief such are the principal facts which may be advanced *pro* and *con* in the doctrine of hereditary tuberculosis. In spite of the great number of works published on this subject, the answer to the questions which we had to solve has not yet been given. It seems to be perfectly well demonstrated by the observations of Landouzy, Queyrat, Hayen, Damaschino, and Lannelongue that tuberculosis is far from rare in young children, and that children born of infected parents are attacked by the disease with alarming frequency. The transmission of the bacilli is also established by a few observations; but facts of this kind, when submitted to severe criticism, as was done by Dr. Küss, appear to be altogether exceptional. In the majority of cases parents suffering from tuberculosis transmit to their children nothing more than a predisposition to contract the disease. The children are born with paratubercular alterations, and some of their organs do not attain full development. But they are not tubercu'ous. Schreiber, Hutinel, and Landouzy injected tuber-

culin into children born of tubercular parents without ever obtaining the characteristic reaction. Inheritance of the germ itself is, therefore, the exception.

The same conclusions seem to be reached as regards leprosy.[1] Danielssen, Böck, and Zambaco attach some importance to the hereditary transmission of this disease. On the other hand, Zambaco admits a tardy heredity and holds congenital leprosy to be altogether exceptional. It is well to note, however, that there is not a single case in which bacteriological examination was made. In most instances marriage of leprous individuals leads to sterility, abortion, and non-viability. The children are weak and cachectic and die under age.

Dystrophies of Infectious Origin. Infection of the parents, and particularly chronic infection of the mother, may impose upon the fetus a defective nutrition. The result is a series of new disorders which may be included under the name of parainfections. In some cases one of the two parents is convalescent from a more or less grave infection at the moment of conception; the product is then a weakling, developed imperfectly and predisposed to contract various infections, notably tuberculosis. In syphilis especially numerous examples of parainfectious disorders are observed. Prof. Fournier has made a perfect study of these which we shall sum up in a few words.

In the first place, there is a fetal cachexia which causes death at a more or less advanced period of gestation. If the fetus does not die it may be born prematurely; at all events it comes into the world as a weakling which develops very slowly. The dystrophy is expressed after birth by incomplete growth; evolution is retarded; the teeth do not appear at the regular periods; the evidences of puberty are delayed; menstruation is not established; the beard is absent. The individual remains imperfectly developed; the genital organs, testicles, and penis are rudimentary; the bones are not sufficiently rich in calcium salts; the brain is often atrophied; the intelligence is more or less dull. A third group of facts is represented by congenital deformities: syphilis is often found in the parents of individuals suffering from club-foot, spina bifida, harelip, and microcephalic and hydrocephalic conditions. Finally, the children of syphilitic parents are predisposed to certain affections of nutritional

[1] Dom Santon. La Léprose, Paris, 1901.

order or of infectious origin. Although Parrot erred in considering rickets a manifestation of syphilis, there is no doubt that this affection is very frequent among children of syphilitics. In this case, however, the manifestation is of the paraspecific kind: syphilis has simply played the rôle of a predisposing cause. Its influence in the appearance of nervous affections, such as Little's disease, or in the more or less early development of tuberculosis and in the occurrence of meningitis should be interpreted in this manner.

What we have stated in regard to syphilis may be repeated with reference to tuberculosis. We find the same difficult, incomplete, and slow development in children. Their stature may sometimes be high, but their bones are fragile, their articulations are clumsy, their muscles thin. The skin is thin and transparent; the hair long and silky; the genital organs imperfectly developed; the fingers are slender, and the nails hypertrophied. The thorax is flat and narrow; the lungs small and often emphysematous; the liver is lobulated. Brehmer and Beneke have noted the weakness of the arterial system, stricture of the aorta and of the pulmonary artery. These children are predisposed to chlorosis and hysteria. Some of them succumb very young, being carried off by convulsions. It is not rare to observe several children die under age, before tuberculosis has clearly manifested itself in the parents.

Congenital Predisposition and Immunity.

Heredity accounts for a great number of facts concerning predisposition and immunity. Some families contract certain infectious diseases with the greatest facility and during several generations. Certain families are particularly subject to tuberculosis, diphtheria, scarlatina, or erysipelas. On the other hand, there are immunities of families, communities, and races. It is certain, for example, that the infections imported into countries where they were unknown prove extremely fatal. Such is the case with syphilis and the eruptive fevers. On the European Continent these diseases are relatively benign, owing to ancestral impregnation. There is created in individuals a certain degree of immunity, or at least resistance, which is transmitted to successive generations.

This leads us to study the immunity which may be acquired by the fetus *in utero*. As has been remarked by Vaillard, two events are possible: the mother may contract the disease during gestation, or one of the two parents may be diseased before fecundation. In

the former case the fetus participates in the disease either because the microbes pass through the placenta and invade it or because the placenta forms a perfect filter against the figurate elements and allows only the soluble products to pass. Then disease of the fetus, complete or incomplete, occurs, and the immunity is similar to that established in the adult. In the latter case, on the contrary, the disease having been cured at the moment of conception, there is merely transmission of an acquired character. The immunity conferred upon the fetus by a disease of the mother is a result established by numerous observations. As has already been stated, a child born of a mother afflicted by variola, and coming into the world without any appreciable manifestation of the disease, may nevertheless have acquired immunity against this infection. Vaccinia behaves in the same manner, at least in certain cases, since the results are quite variable. Burckhard experimented upon eight children; four of them were born of women who had been successfully vaccinated during gestation. The children proved immune, one of them continuing to be so at the end of six months. In two cases revaccination gave a doubtful result, and one of the two children born of these women proved refractory. The author likewise observed that one of the two children born of mothers who had been revaccinated without success at the end of their pregnancy proved refractory. The results obtained by Chambrelent were almost identical. This author vaccinated forty women; he obtained a true vaccinia in the children only seven times. We find quite different figures in Behm's researches. Out of twenty-nine children observed by this author, only two proved refractory. Finally, Wolff, having successfully vaccinated seventeen women, vaccinated with equal success all the children from one to six days after birth. On the other hand, Lopp observed vaccinal immunity in children, but this immunity did not last more than from six to eighteen months. These contradictory results point to the conclusion that vaccinal immunity, like infection itself, is transmitted only in about half the cases.

One of the human diseases which has served most for the study of these important questions of general pathology is syphilis. We have already pointed out that a woman bearing a syphilitic fetus, even when she does not contract the disease, becomes immune against the infection; she may with impunity suckle her child which would contaminate a strange nurse. This is what is called Colles' law. This law is confirmed by an experiment of Caspary: A woman

fecundated by a syphilitic man, who was apparently cured, aborted at the sixth month. The mother, who had presented no specific manifestations at any time, consented to be inoculated, and proved to be immune. In other cases the result is different: the fetus does not communicate immunity to the mother, but the disease itself. This is called *syphilis by conception.* Diday was one of the first to draw attention to these facts, the number of which at present is quite considerable. Syphilis by conception runs its course like congenital syphilis. In both instances infection is effected through the blood. The pathogenic agent penetrates directly the circulatory system. Hence, the absence of all primary manifestations. A pregnant woman will then present symptoms of secondary syphilis without ever having either chancre or enlargement of the lymphatic glands.

Profeta has formulated a law similar to that of Colles. If a child born of a syphilitic mother is found in sound condition it has acquired immunity against syphilis and does not contract it through the milk or caresses of the mother. This is a result analogous to that observed in other infections, for example, variola.

Among the experimental diseases anthrax is the one that has been the subject of the most interesting investigations bearing upon these questions. Chauveau, after having inoculated Algerian sheep at the end of gestation, observed that the young born of them presented no morbid symptoms when they were inoculated with the bacillus. This is a new illustration of the immunity which may be acquired by the fetus. Anthrax has also been employed to demonstrate experimentally the truth of Colles' law. Lingaard inoculated this disease into fetuses of rabbits while yet in the uterus. The young died, while in most cases the mothers survived. Microscopic examination and cultivation revealed no bacilli in the maternal organisms, and yet the animals had acquired perfect immunity, which still persisted at the end of eight months. The fact is the more interesting, as all experimenters are aware how difficult it is to vaccinate the rabbit against anthrax. Moreover, Lingaard established that, in order to confer immunity, the fetus must be inoculated at least thirty-six hours before its expulsion; the other fetuses may become refractory if the inoculated young remain six days in the uterus. In some instances, as in syphilis by conception, the mother contracts anthrax infection; but then placental alterations, through which the passage of the bacilli may be traced, exist. When the mother resists

the pathogenic agents have their seat exclusively in the fetal blood-vessels of the placenta.

On the basis of these experimental facts Chauveau established his famous theory of immunity. After the experiments of Brauell and of Davaine, the placenta was supposed to constitute a perfect filter; immunity was attributed to the transmission of soluble substances produced within the maternal organism under the influence of anthrax. It is at present known that the placenta is in some cases traversed by anthrax bacilli, and, therefore, Chauveau's deductions have been questioned. It has been asked whether congenital immunity is not due to the passage of the bacilli which are too small in number to kill the fetus, but sufficient to vaccinate it. To this objection Chauveau answered that the passage of the bacilli through the placenta is an inconstant phenomenon, while in all his experiments, forty in number, the young had acquired immunity.

The most important experiments from the standpoint of hereditary transmission of immunity are those in which animals were vaccinated by living microbes or by soluble products more or less long before fecundation. The experiments pursued with symptomatic anthrax had already demonstrated that animals born of mothers vaccinated even some time before fecundation often prove refractory (Arloing, Cornevin, Thomas).

Studying the transmission of immunity in animals vaccinated against vegetable poisons, such as abrin and ricin, or against tetanus, Ehrlich arrived at the following conclusions: The father does not communicate immunity to his offspring; the mother may impart a transitory immunity which lasts three or four weeks and is not transmitted from generation to generation. This is a passive immunity due to intraplacental passage of antitoxin contained in the maternal organism. By studying diphtheria, Wernicke reached identical results. On the other hand, Tizzoni and Centanni, experimenting with tetanus and hydrophobia; Charrin and Gley with the bacillus pyocyaneus reached the conclusion that the male is equally apt to transmit immunity. There was, therefore, hereditary transmission of a character acquired by the somatic cells. The question was taken up by Vaillard in a work which may be held as a model of fine experimental criticism. Animals were vaccinated against tetanus and cholera by means of soluble products and against anthrax by means of living microbes. When a strong immunization was obtained the animals were mated. The young born of a hypervac-

cinated father and a normal mother never presented the slightest degree of resistance. The vaccinated females invariably communicated to their offspring the immunity which they had acquired. But immunity thus transmitted is not permanent. It may, however, be prolonged by lactation; the mammary secretion furnishes some antidote to the nursling. This second factor seems to play the more important rôle. The researches of Vaillard tend to show, however, that we must not rely too much upon lactation, for milk is active only in certain animal species, the mouse, for example.

Three theories have been advanced to explain the intrauterine transmission of immunity. Duclaux, Arloing, and especially Charrin and Gley have advanced a cellular theory. According to these authors the cells acquire a certain activity under the influence of vaccination; the cells of generation, influenced like the other cells, impart their mode of life to the being which is developed; the daughter cells continue the physiological activity of their mother cells, and, like these, they are capable of secreting germicidal or antitoxic substances and exercising phagocytic action. This theory well explains the transmission of immunity by the father; but we know that the view is disputed and rejected by the majority of authors.

The second theory is that of Ehrlich, according to which the immunity of the fetus is due to the passage through the placenta of antitoxic and germicidal substances from the mother. This theory would evidently be annihilated if it was demonstrated some day that the father also may transmit immunity. According to Ehrlich, the mother alone has this power, and the immunity of the fetus is a passive one, analogous to that obtained outside of the uterus by means of serumtherapy. Vaillard admits the passage of the active substances of the serum through the placenta, but, following the ideas of Metchnikoff, he does not accept the theory that immunity is effected only by means of the fluids of the organism. He remarks that there is not always a relation between the state of the fluids and the degree of immunity and believes that the active substances of the mother, passing through the placenta, stimulate the fetal organism, render the cells insensible to intoxication, increase the energy of the phagocytes, and even give rise to the secretion of antitoxins. This is to extend to the fetus the general theory which is accepted by some authorities concerning immunity. Without dwelling upon the discussion, we shall only note that the present tendency

is to attribute immunity, as has already been maintained by Chauveau, to the intraplacental passage of soluble substances. Fetal immunity is comparable to that produced by a preventive injection of serum; it is, perhaps, a little more lasting, since the impregnation is longer, but, like all passive immunity, it rapidly disappears.

Conclusions. Summing up the principal results arrived at, we see that several results are possible. In some cases the microbes produce in the fetus a graver infection than that of the mother. By vaccinating pregnant sheep we often see the fetus die and expelled by an abortion. The death of the fetus killed by the infection which is resisted by the mother explains a certain number of abortions observed in the human species, for example, in pneumonia, typhoid fever, and syphilis.

Not infrequently, the fetal disease is similar to that of the adult. Such, in some cases at least, are variola and syphilis. In other instances the fetal affection differs not by its anatomical characters, but by its peculiar localization. Such is the case in congenital tuberculosis, which invades particularly the liver. It may be said that in almost all fetal infections the liver is most profoundly affected and contains the greatest number of pathogenic agents. This is readily conceivable in view of the fact that this gland is placed like a barrier at the root of the bloodvessels coming from the placenta. There are diseases in which the fetus contains pathogenic microbes without the existence of any appreciable lesions. Thus, as has already been stated, in anthrax the blood does not present the agglutinating character which is so manifest in the adult. In typhoid fever the fetus does not present the alterations in Peyer's patches nor splenic hypertrophy.

It is also possible that a child born of an infected mother presents at birth no morbid manifestations, but, after several years, symptoms of this infection may become manifest. This has been demonstrated in syphilis, and is supposed to be true of tuberculosis. In other instances the infections of the parents may impose upon the fetus an abnormal mode of nutrition which may persist throughout life. Dystrophies, congenital malformations, and predisposition to the most varied infections may result. However, infections of the parents do not always produce disturbances in the children. There are cases in which heredity is not evidenced by any morbid symptoms. In these instances the child may be influenced by the maternal disease and acquire immunity. This intrauterine vaccination is

inconstant. In a last category of cases, we place those instances in which the child comes into the world uninfluenced by the parental disease.

Such are the principal eventualities that may be observed. We see that the results are widely variable, from the grave and rapidly fatal infection to the absence of all symptoms, and even of all morbid impregnation.

CHAPTER XXI.

DIAGNOSIS AND PROGNOSIS OF INFECTIOUS DISEASES.

Various Procedures of Diagnosis. Clinical Procedures. Bacteriological Procedures. Research of Pathogenic Agents by Microscopic Examination and by Cultivation. Inoculations from a Diagnostic Standpoint. Cytological Examination of the Blood, Fluids, and Exudates. The Vesicatory Test. Diagnosis According to Chemical Modifications in Fluids. Research of Agglutination. Modifications in the Urinary Secretion. The Diazo Reaction. Diagnosis by Therapeutics. Diagnosis by Microbic Toxins. Tuberculin and Mallein. Diagnostic Problems. Questions Concerning the Seed and the Soil. Importance of a Complete Diagnosis for Prognosis. The Bases of Prognosis. Personal Statistics: Mortality in 8832 Cases of Infectious Diseases. Influence of Age and Sex upon Mortality. Variation of Gravity According to Various Epidemics. Importance of Etiological Conditions and of Mode of Invasion. Bases of Prognosis during the Stationary Period. Study of the Local Lesion, General Phenomena, and State of the Principal Organs. Importance of Previous Diseases and Lesions for Diagnosis. Prognosis for the Present, for the Future, and for the Descendants. Comparison of Clinical and Bacteriological Methods.

THERE are two methods for establishing diagnosis—one, clinical, the other the laboratory method. The clinical method consists in inquiry as to the sensations experienced by the patient, the disturbances that may be seen, and the physical signs that may be detected. It is customary, however, to complete the information thus obtained by two more scientific procedures, namely, the determination of the temperature by means of the thermometer, and chemical analysis of the urine.

The advance in bacteriology and the importance recently acquired by experimental investigations have led to other procedures. It has been asserted that clinical investigations are absolutely inadequate. It has been said that in order to succeed in determining the nature of a malady it is necessary to resort to methods of precision, to search for bacteria in exudates, secretions, and excretions, and to study the chemical and histological modifications in the organs, tissues and fluids. The consequence is that, in a great number of cases, it is possible to make a diagnosis without examining the patient. It suffices to look for Koch's or Loeffler's bacillus in order to diagnose tuberculosis or diphtheria. It is in no wise pretended to cast doubt upon the service which may be rendered clinicians by laboratory researches, but simply to say that these

two methods are not to be opposed to each other. Some authors have recently taken certain pleasure in pointing to the errors of clinical diagnosis. They seem to be happy to demonstrate that the old methods give but illusive information. For some physicians the diagnosis of diphtheria is absolutely impossible without cultivation in serum. It seems to me that this tendency leads to deplorable conclusions in practical medicine. It should not be overlooked that in many cases the physician cannot possibly resort to new methods. A practitioner in a country place, for example, far from scientific centres, can hardly have the facilities for making cultures. If it is a case of acute infection, and if, guided by new ideas, he sends the suspicious exudates to the nearest faculty, the chances are that he will receive an answer when the evolution of the disease is at an end—*i. e.*, when the patient has recovered or is dead. This does not mean that scientific data are to be rejected. Those who are practising in cities possessing laboratories, and especially those who attend in hospitals, must resort to modern methods of investigation. This, however, should not be done with the idea of opposing the results furnished by cultivation to information given by clinical observation—to show the superiority of the former and the uncertainty of the latter. He who can combine observation and experimentation must decide what modifications must be introduced into nosological classification and give greater precision to simple observations. Bacteriology must be resorted to, not to show the insufficiency of clinical observation, but as a means of more closely approaching the truth. Those who have a hospital with a laboratory at their disposal must compare the results furnished by different procedures of exploration, and, far from bringing out their antagonisms, seek to harmonize them. It seems to me that we must not as yet ask too much of bacteriological data. We shall presently show that they sometimes furnish indications less certain than those yielded by simpler procedures of exploration.

Search for Pathogenic Agents by Microscopic Examination and Cultivation. The means now at our disposal for making a scientific diagnosis may be divided into three groups: the search for microbes, the study of modifications in cells and fluids, and the specific action of certain toxins.

The search for microbes is made by microscopic examination, cultivation, and inoculation into animals. Microscopic examination is applied to secretions, dejections, and inflammatory foci; more

rarely to the blood and the interstitial fluids of organs. It renders very remarkable service in determining the nature of an inflammatory lesion, an effusion into a serous cavity, an abscess, and a gangrenous focus. When a focus does not communicate with the exterior—*i. e.*, when it has not been invaded by common bacteria from without, one may be nearly certain that when a microbe is found it is the agent of the morbid process. At any rate the procedure is very simple, and the harmlessness of exploratory puncture justifies this sort of investigation in most cases. On the contrary, when the morbid focus is not closed, it generally contains several microbic species. Hence, interpretation becomes far more difficult. In some cases a clearly differentiated specific bacterium is found and is responsible for the morbid phenomena. Such, for instance, is the case when actinomyces are detected in a purulent fluid or the tubercle bacillus in sputa. The result has no importance, however, except when it is positive. The absence of Koch's bacillus in a sputum does not at all imply the absence of tuberculosis. Nevertheless, the scientific character of these researches gives an exaggerated importance to the results obtained. The fact that the bacilli are absent from the sputum when the morbid foci are closed is too easily overlooked. Errors inherent in defects of technical methods must also be remembered. Examination for bacilli, simple as it is, none the less requires a certain amount of experience. I saw a patient with syphilitic antecedents suffering from manifest pulmonary tuberculosis. The physical signs left no doubt whatever as to the diagnosis. He had been given for several weeks, and to his detriment, large doses of potassium iodide. His physician, a very able man, who had instituted the treatment, had based it upon the absence of Koch's bacillus in the expectorations. There had certainly been some technical error, for when I examined the case I found the sputa nummular and swarming with tubercle bacilli. Such errors are not rare. I could cite several examples of a similar character.

When the bacilli are present, certainty is established. When, however, the parasites are few in number, doubt still remains. We know that Koch's bacillus may vegetate upon certain mucous membranes as an inoffensive parasite. Its presence does not necessarily imply the existence of a tubercular lesion. Such is the case with the tonsil, which often contains bacilli, but is seldom affected by them. The difficulties are far more considerable when less clearly

specified bacteria are looked for. For example, expectorations are examined and streptococcus, pneumococcus, Friedländer's bacillus, tetragenes, and various spirilla are found. What right have we to conclude that such and such a microbe, to the exclusion of others, is the cause of the morbid manifestations? If one species predominates, the probabilities are that it is the pathogenic agent. There is, however, no absolute certainty, and we have already seen, with reference to anginas, how difficult interpretation is in the majority of cases. Thus, in chancriform tonsillitis an association of spirilla and fusiform bacilli, which are of great diagnostic value, are found The same association, however, may be met with in other clinical types and even in syphilis. Such was manifestly the case with secondary tonsillar lesions of very difficult diagnosis.

When bacteria are found irregularly disseminated a decision is impossible. Hence, for the diagnosis of anginas, another procedure is resorted to—cultivation. The point to be settled is, in general, whether an angina is or is not diphtheritic in nature. As Loeffler's bacillus rapidly vegetates in gelatine serum and develops in this medium sooner than other bacteria, the method becomes very simple. A particle of the suspicious exudate is spread upon gelatine serum and is placed in the incubator. At the end of twelve hours the bacillus of Loeffler, if present, produces colonies. This mode of action is usually not objectionable. It must be noted, however, that in certain cases the development of the bacillus is more tardy. It sometimes takes twenty-four or thirty-six hours. On the other hand, while there is no doubt when the colonies are abundant and rich in bacilli, it may still be a question whether an angina should necessarily be regarded as diphtheritic simply because Loeffler's bacillus has been detected by serum culture. If another medium had been employed, a different result would have been obtained. If, for instance, the cultivation had been made in bouillon the streptococcus might be present and Loeffler's bacillus absent. What right, then, have we to conclude that the angina was diphtheritic? Why should the results furnished by cultivation in one medium be more valuable than those obtained in another? Why prefer serum to agar-agar or to bouillon? Why accept Loeffler's bacillus and ignore the streptococcus, which is just as harmful?

An attempt has been made to avoid the difficulty by the admission of a hybrid form having particular clinical characters, which has been designated strepto-diphtheria. This reasoning is open to

criticism. In order to admit this form the development of two bacteria in blood serum is required. It is hard to conceive why an important rôle is attributed to the streptococcus solely on the ground that it develops in serum. Its multiplication in this medium does not at all prove its virulence. Even though we admit that the procedure is exact, other difficulties arise. What conclusion is to be drawn in those cases in which cultivation gives only scanty colonies of the diphtheria bacillus? It is known that this bacillus quite often vegetates in the normal mouth. When it is encountered in culture it may be asked whether or not we have to deal with an inoffensive parasite. Moreover, although this bacillus is readily recognized, there is a short bacillus, the nature of which is in no wise determined as yet, which is considered by some as a variety of the diphtheritic bacillus, and by others as a particular microbe. In this case, bacteriological diagnosis is indecisive.

Referring to the results which we have described in treating of microbic associations (p. 145), it may be noted that in thirty-one cases of anginas studied comparatively by direct examination and by cultivation in agar-agar and serum, we constantly found Loeffler's bacillus in the last-named medium, while we detected it in only half of the cases by direct examination or by cultivation in agar-agar. Moreover, in these thirty-one patients the exudate contained streptococci visible by direct examination nine times; cultivation in agar-agar revealed them sixteen times, and cultivation in serum three times only. Still, in one case in which the streptococcus developed in serum, agar-agar showed only the tetragenus.

These reflections are by no means intended to discredit the results furnished by bacteriology. They are intended only to call attention to the disposition of many authors to attribute an absolute value to the data of cultivation. A vast amount of research is yet required in order to base a description of anginas upon a parallel study of their clinical aspect and experimental results. I have dwelt upon anginas because these are the affections the study of which has most profited by modern bacteriological investigations. We possess no selective medium analogous to blood serum for the other pathogenic bacteria. The preparation of media for the cultivation of specific bacteria in the midst of common parasites has not given gratifying results.

The employment of peptone-water is useful in the diagnosis of cholera, but the detection of Eberth's bacillus in fecal matters is

far more difficult. Elsner's formula does not seem to respond to the purpose in view.

Bacteriological examination is of considerable interest in connection with sexual diseases. Examination for the gonococcus is daily practised and serves to establish the diagnosis of gonorrhea. It is well to remark, however, that recently there have been found in the suppurations of the genital organs anaërobic microbes which have nothing in common with the gonococcus, but it is very difficult to recognize them by a simple microscopic examination.

When the process is one of common suppuration two cases are possible: The focus may be closed or open. When it is closed a puncture is made into it and a specimen of the fluid is submitted to microscopic examination and to cultivation. The data obtained have undeniable value, provided the results of direct examination be carefully compared with those furnished by cultivation. If by both of these procedures a single species is found, certainty is almost absolute, but not complete, since it is possible that the true pathogenic agent may be unrecognizable by our present methods of staining and cultivation. This possibility is becoming less and less as bacteriology advances, and the result is perfect in most cases. The result is also satisfactory when several species of microbes are found. If, however, a great number of different bacteria are revealed by microscopic examination, and if cultivation shows only one or two, the difficulties are the same as in the case of angina. Such is the case with gangrenous foci. Anaërobic cultures have greatly aided the study of this morbid process, but by a natural reaction too much importance has been attributed to anaërobics. In most cases putrefactive microbes do no more than complete the work already begun. They putrefy tissues altered by other microbes, and notably by aërobics. Moreover, we must remember that the latter may of themselves produce certain gangrenes which are sometimes of benign character.

When an open focus is examined the results are very clear if only one species of microbe is found. If several species are detected, the difficulties of interpretation are the same as in the case of angina. In some cases, however, the presence of certain morphological elements is of paramount importance. Thus, whether the lesion be open or closed, the presence of yellow grains resembling flowers of sulphur establishes the diagnosis of actinomycosis.

The associated microbes are then of little consequence; the nature

of the lesion is well determined, and furnishes accurate indications for treatment.

The microbe may likewise be looked for in fluids, secretions, or natural excretions, or even in the organs. In this connection the blood, urine, fecal matters, and cerebrospinal fluid are examined. Capillary punctures into the viscera are practised, particularly into the spleen. By microscopic examination of the blood it is possible to recognize certain absolutely characteristic specific parasites, such as the spirilla of recurrent fever and the hematozoon of malaria. The search for the hematozoon is not always easy, but when it is positive the result has considerable importance from a practical standpoint. It permits elimination of symptomatic intermittent fevers and gives a solid basis for treatment. As we have already stated, special corpuscles are found in the blood of variola patients by simple microscopic examination. These corpuscles are particularly numerous in the hemorrhagic form. In the suppurative forms they are seen at the beginning of the disease, at the period when diagnosis is difficult. In most bacterial diseases microscopic examination reveals no bacteria or reveals them only at a more advanced stage when death is approaching. In the case of anthrax and of septicemias the blood is not invaded until death is near. It is not so, however, with methods of cultivation, which may give positive results at a less advanced period of an infection, provided cultivations be practised on a large scale. According to the procedure employed by Davaine, 1 c.c. of blood must be taken from a vein and placed in appropriate media.

Examination for microbes in the urine is seldom practised. It is a difficult procedure. If a simple microscopic examination is to be made, the urine must be centrifuged and the deposit examined. If cultures are to be made, the urine must be drawn by aseptic catheterization, which requires a great deal of practical experience in order not to be misled by accidental contamination. The study of fecal matters is not less difficult. In certain cases, however, microscopic examination renders service by showing a common microbe predominating or by revealing a specific agent. Thus, the tubercle bacillus may be found in the excrements, and this fact is of great importance, since bacilli which have been ingested do not pass into the fecal matters. The presence of Koch's bacillus in the feces, then, permits affirmation of the existence of intestinal tuberculosis. In dysentery examination of the dejecta it is likewise

necessary, for it enables us to determine whether or not the case is one of amebic dysentery.

In recent years the search for microbes in the cerebral spinal fluid has acquired great importance. Lumbar puncture being an inoffensive operation, we easily conceive how serviceable this method of exploration may prove. The search for microbes in the organs requires greater precautions. Puncture of the liver, once quite frequently practised for the diagnosis of typhoid fever is rather an uncertain method, and can hardly enter into current practice.

Inoculations from a Diagnostic Standpoint. The difficulty of attributing morbid manifestations to one form of pathogenic bacteria rather than to another has suggested the method of inoculation into animals. It was even hoped that this method would enable us to give a positive prognosis. It was thought that a relation existed between the evolution observed in man and the effects produced by experimental inoculation. Such a relation undoubtedly exists in a certain number of cases, but not in all. As regards the streptococcus particularly, the results are absolutely deceiving. Cultures prepared with blood taken immediately after death have often been injected in large doses without producing the slightest disturbance. Among observations which I have collected, the following may be cited. 1. Pulmonary gangrene ending fatally; the fluid contained in the lungs presented especially streptococci. When directly inoculated into the veins of a rabbit in the dose of 1 cubic centimetre, it produced a chronic disease characterized by paraplegia and retention of urine, ending fatally at the end of two months. The cultures injected into the veins in the dose of 5 c.c. gave rise to no disorder. 2. Streptococcus obtained from a newborn which had succumbed to erysipelas of the navel; the first culture, when injected into two rabbits in the dose of 5 c.c., caused no morbid manifestations. 3. Streptococcus obtained from an aged man dead of erysipelas; same experiments, same results. 4. Streptococcus obtained from dead of puerperal fever; same experiments, same results. These few facts once more demonstrate how difficult it is to apply to man conclusions drawn from experiments performed upon animals, and how uncertain is determination of virulence, at least in the case of the streptococcus.

It is true that a great number of observations have been published which seem to establish that, in cases of angina, inoculation into animals may furnish interesting data. For example, when we find

a bacillus presenting the characters of the diphtheria bacillus, the nature of which is not quite well determined, it is incontestable that inoculation may elucidate the problem. Thus, at the necropsy of a diphtheritic case, I found an hepatic abscess containing a bacillus analogous to Loeffler's. In order to establish a more certain diagnosis, I inoculated two guinea-pigs. One was kept as control and rapidly succumbed; the other, which received at the same time antidiphtheritic serum, remained in good health. In this instance the demonstration is unassailable.

While inoculation solves the problem when a single species of bacterium is detected in a focus, it may furnish doubtful data when several species of microbes are encountered. If one of these is inoculated and found to be pathogenic, it cannot be concluded that it was the cause of the accidents, for the agents unconsidered were perhaps just as virulent. Therefore, in order to form a conclusion, it is necessary to inoculate all the microbes isolated—a task representing considerable labor—and still the result would be disputable, for the reason that it is possible that the specific microbe will not develop in the particular medium employed, either because this medium is not favorable for it or because the other bacteria prevent its multiplication. I recognize, however, that inoculation into animals may be of very great service. For example, a polymicrobic culture is obtained. By injecting it into an animal we may see a bacterium predominate, and it will then be possible to obtain a pure culture after one or two passages through animals. Of course, it would not yet be safe to draw an absolute conclusion. Nothing proves that the microbe which is the most harmful for the animal was the one most harmful for man. Here, therefore, is a method that renders remarkable service to the experimenter rather than to the clinician. Confining ourselves to the domain of clinical diagnosis, we find various infections the diagnosis of which may be facilitated by inoculation. These are the pneumococcic infections, anthrax, glanders, tuberculosis, hydrophobia, and, less frequently, gaseous gangrene and tetanus.

When the pneumococcic nature of a lesion is suspected, an inoculation is made into the mouse. The animal succumbs within twenty-four or forty-eight hours, and examination of the blood shows characteristic capsulated diplococci. It is well to remember, however, that this bacterium is often encountered in the saliva of healthy individuals. The positive result of this inoculation cannot, there-

fore, lead to an unquestionable conclusion. When a lesion is suspected to be of anthrax, diagnosis may be a matter of difficulty, for the reason that malignant pustule often contains very few bacteria, and, therefore, experimental inoculation is negative.

In a case in which the diagnosis was difficult and which terminated in recovery I inoculated four guinea-pigs with the serum of the vesicles. One of these animals died of anthrax, thus demonstrating the nature of the lesion which, without inoculation, might have been interpreted in a different manner.

The diagnosis of glanders often presents great difficulties. An experimental method has, therefore, been long looked for. The ass first served for purposes of experimentation. When this animal is employed the operation is performed in the following manner: After shaving the forehead, cutaneous scarifications are made, and then the suspicious pus is rubbed upon them. From the tenth to the fourteenth day the general phenomena appear, and the animal soon dies of bronchopneumonia. The necropsy reveals glanders granulations in the viscera. Instead of the ass the dog may be employed. The same method is resorted to, and four or five days after inoculation a glanders ulcer appears which subsequently heals. Christot and Kiener proposed a simpler procedure. They advised inoculation into the guinea-pig. The animal died in eight or ten days with characteristic lesions. The best method is that of Straus. The suspicious pus is injected into the peritoneum of a male guinea-pig. At the end of forty-eight hours a testicular vaginalitis develops. The skin of the scrotum becomes red and the two layers of the tunica vaginalis adhere by a purulent exudate. The testicle and epididymis are seldom involved. This method is good, but not perfect. The pus may contain various bacteria capable of producing a fatal peritoneal septicemia. Hence, it is advisable to inoculate two guinea-pigs, one beneath the skin, the other into the peritoneum. On the other hand, various pyogenic microbes behave like the bacillus of glanders (Nocard). The result of inoculation must, therefore, be controlled by bacteriological examination and cultivation.

Examination for the tubercle bacillus is so easy that inoculation is seldom necessary. In cases of local tuberculosis, however, and in those pulmonary lesions in which favorable evolution seems to remove all suspicions as to the tubercular nature of the process, as well as in pleuritic effusions, the bacilli are so few in number that there is great danger of not detecting them by microscopic exami-

nation. In such instances inoculation is most serviceable. The inoculation must be practised upon the guinea-pig, which is the animal most sensitive to tuberculosis. Survival is very long; it often exceeds five or six weeks, and at times the animal may live for several months or even a year. The early development of adenopathies is significant. Six or eight days after inoculation the lymphatic glands corresponding to the point of inoculation become congested, and other glands are later involved. These multiple and progressive glandular affections are absolutely characteristic. The method may, therefore, be of use, notably in cases of serous pleurisy.

As is known, the diagnosis of hydrophobia is a matter of great difficulty. Even at the necropsy a retrospective diagnosis cannot be made. No characteristic lesion is found in the viscera and tissues. This fact is of considerable importance in practice. When an individual is bitten by a rabid dog it is too often the custom to kill the animal and then send the cadaver to a veterinary physician for necropsy. Great diagnostic value was formerly attached to the presence of foreign bodies in the stomach of rabid dogs. These animals bite and swallow anything they encounter. Hence, substances which are not usually among the contents of this organ, such as pieces of wood, straw, earth and gravel, are found in their stomachs. It has been demonstrated, however, that these findings are of no diagnostic importance. Such substances are likewise found in non-hydrophobic dogs. In view of the investigations of Van Gehuchten, histological examination may, perhaps, give better results. But such researches are delicate and require accurate knowledge of histology. For the time being the study of symptoms seems to me to be of greater importance. Hence, this practical conclusion: No dog which has bitten a person should be killed; but it should be confined and carefully observed. This is the only means of learning at the end of two or three days whether it is hydrophobic or not. Moreover, the circumstances under which the biting occurs furnishes a presumptive basis. It may be said that a dog which bites without provocation and without any appreciable cause is generally rabid. If the animal has been killed, the only means of obtaining conclusive information is inoculation. This operation is generally performed upon the rabbit. The emulsion obtained with the medulla is injected beneath the dura mater. The operation is extremely simple: The animal being firmly bound, and, if necessary anesthetized, an incision is made into the skin.

The cranium is opened by means of a smal trepan, avoiding the upper longitudinal sinus. The hemorrhage produced by incision of the bone is generally quickly arrested. Then, by means of a curved canula adjusted to a Pravaz syringe, the dura mater is punctured and a few drops of the emulsion are injected beneath this membrane. The canula is withdrawn, the wound sutured and covered with iodoform collodion. Under these conditions the animal contracts hydrophobia after a period of incubation varying from twelve to fifteen days. To ensure the production of hydrophobia, it is not absolutely necessary to resort to the procedure just described. Introduction of the virus into the anterior chamber of the eye gives nearly as certain results. The same is true when the inoculation is made into any nerve whatever, for example, into a peripheral nerve. Galtier, Di Vestea and Zagari have shown that the sciatic nerve offers a very reliable route of introduction. Finally, when a contused wound contaminated by foreign bodies or earth becomes the starting point of morbid manifestations, the inoculation into a guinea-pig of the fluid discharged from the lesion or, still better, of a particle obtained by scraping, may reveal, within forty-eight hours, the presence of the microbe of gaseous gangrene or of tetanus.

Cytologic Examination. A new method of diagnosis consists in searching for certain reactions produced in the organism by pathogenic agents. The attention of observers was first attracted by the blood. In fact, from the start of infections this fluid undergoes profound modifications, some of which bear upon the cellular elements and may be detected under the microscope. We have already stated that the variations in the white blood corpuscles enable us to follow the evolution of infections, and at times to foretell their course and announce relapses. These observations less frequently serve the purposes of diagnosis. Nevertheless, the researches of Courment and Montagard and those pursued at the same time by Dr. Weil in our wards show that the leucocytic formula of the blood presents particular characters in variola. The results are so clear that we often resort to this procedure in order to settle diagnostic difficulties. It must be remembered, however, that varicella and variola produce analogous modifications in the blood. The method mostly serves to differentiate variola from other eruptive fevers and various pyogenic infections which simulate it.

The examination of the cells may be made not only in the blood but in other fluids and exudates. Examination of the cerebro-

spinal fluid and of effusions produced in various serous membranes has led to a cyto-diagnosis the importance of which has been well shown by Widal and Ravaut.

In cases of primary tuberculosis of the pleura pleuritic effusion is remarkable for the almost exclusive presence of small lymphocytes. In individuals afflicted with cancerous or ulcerating lesions of the lungs, or hydropneumothorax, numerous altered polynuclears are found, while in mechanical pleurisy the endothelial cells of the pleura predominate. In the case of streptococcic pleurisy neutrophilic polynuclears are almost exclusively present. In pneumococcic pleurisy the greater part of the cells is represented by polynuclears and large mononuclear cells mixed with red blood corpuscles and a few lymphocytes.

The Vesicatory Test. These researches are applicable only to certain special cases. Hence, it seemed to me to be interesting to determine the cytologic formula of effusions which may be produced in man by the application of vesicatories. The examinations which we made with Dr. Josué[1] established that the vesicle produced by a vesicatory holds in suspension a fairly large number of cells. In the normal man a strong proportion of polynuclear eosinophiles is found. In individuals suffering from an infectious disease these cells are less numerous or altogether absent. They reappear if the organism overcomes the infection. The vesicatory test thus furnishes valuable indications regarding the intensity of the toxi-infectious impregnation of the organism and the mode of reaction of the hematopoietic organs. It is readily conceivable what advantage may be drawn from such information from a diagnostic and especially prognostic standpoint. The difference in the results obtained in the healthy man and in the sick must depend upon the action exercised by microbic toxins upon the hematopoietic organs, and notably upon the bone-marrow. Under the influence of these poisons the bone-marrow gives rise to neutrophilic polynuclears. On the contrary, it cannot furnish eosinophiles. Ehrlich has well shown this sort of antagonism which exists between the infectious process and eosinophilia. The application of a vesicatory stimulates the production of eosinophiles, and the examination of the fluid shows in what measure the bone-marrow is capable of producing these elements. The vesicatory test thus enables us to determine the intensity of

[1] Roger and Josué. L'épreuve du vésicatoire. Soc. méd. des hôpitaux, May 3, 1901.

the action of toxins upon the hematopoietic organs. By this method we may judge to what extent the function of these organs is diminished under the influence of the toxic element.

Apart from the eosinophilic polynuclears there are found in the vesicle neutrophilic polynuclears and large and small mononuclears. It is not rare to find in the preparations a certain number of large mononuclear elements containing granulations. These are myelocytes. This fact is interesting, since no such cells are commonly found in the blood or in pathological exudates. They generally remain in the bone-marrow, where they give rise to white globules with polymorphous nuclei or polynuclears. The presence of myelocytes proves that the vesicatory produces a very profound effect upon the hematopoietic organs. Besides the cells above described, all of which are similar to those circulating in the normal or pathological blood, particular elements are found in the fluid produced by the vesicatory. These are cells provided with a thin layer of protoplasm which is colored brownish-yellow by triacid and rose by eosin. Their nucleus, which is round or oval, is stained green by triacid and pale violet by hematoxylin, but is not clearly defined. Unable, as yet, to decide the nature and origin of these elements, we shall designate them "vesicatory cells." Our researches were made upon two normal individuals and twenty-seven patients, eleven of the latter suffering from pulmonary tuberculosis, and three seemingly from tubercular pleurisy. The technique employed was very simple. Twelve hours after the application of a vesicatory of four or five square centimetres, when the bulla was well formed, the fluid was taken, centrifuged, and decanted, and the sediment spread upon slides and dried over the flame. Most of the preparations fixed by heat at 230° F. (110° C.) were stained with Ehrlich's triacid solution or thionin. A few were treated with alcohol-ether and stained with eosin-hematoxylin. The preparations obtained by the triacid stain are the clearest.

In the two normal individuals we found a very large proportion of eosinophiles. In no pathological case did we find such a great number. A count of the various species of cells gave the following figures:

	I.	II.
Neutrophilic polynuclears	65.0 per cent.	77.8 per cent.
Eosinophilic polynuclears	25.5 " "	19.2 " "
Large mononuclears	1.0 " "	3.0 " "
Small mononuclears	8.0 " "	
Vesicatory cells	0.5 " "	0.0 " "

The vesicatory test leads to altogether different results in tuberculous subjects. In cases of common chronic tuberculosis a very great number of polynuclears are found. These reach or exceed 90 to 95 per cent. On the other hand, the eosinophiles are very rare and in most cases are absent. The proportion of large and small mononuclears is quite variable according to the case. That of the vesicatory cells varies between 0.5 and 3 per cent. In one tubercular case (Obs. XI.) the number of the eosinophiles was relatively large. It amounted to 3.2 per cent. This case was not an exception to the rule, for it was a man suffering from a peritoneal localization and from pulmonary lesions tending toward sclerosis. The relatively high percentage of eosionphiles indicated the favorable course of the disease toward recovery.

Furthermore, we have noticed that the cells present a special aspect in tuberculous individuals. They are swollen and much larger than in normal subjects. This particular state of the cellular elements is not absolutely peculiar to tuberculosis, but it is far more pronounced in this infection than in others. Hence, when it is manifest, it may lead to the detection of a latent tuberculosis. This is precisely what happened in one of our cases (Obs. XII.). Having applied a vesicatory to a man whom we considered to be in normal condition, we were surprised to find in the fluid a low percentage of eosinophiles as compared to the normal ratio, and a sufficiently great number of swollen cells. Minute examination of the respiratory organs enabled us to recognize slight but incontestable lesions, which, until then, had produced no functional disturbance. Percussion revealed dulness under the right clavicle and in the left supraspinous region. In the same regions inspiration was harsh and attended by a few dry râles and pleuritic frictions. The relatively high percentage of eosinophiles (7.82 per cent) indicated that the constitution was vigorous—a fact quite in harmony with the results of clinical examination. It may be added that the vesicatory test gives the most valuable information in the beginning of tuberculosis and enables us to appreciate the degree of resistance of the individual and his chances of recovery.

The number of eosinophiles was still larger in two cases of acute serofibrinous pleurisy. This affection may be considered as a local tuberculosis of the pleura tending toward recovery. It would, therefore, be natural to expect to find a formula expressing the resistance of the organism. This is precisely what was found in

Observations XIII. and XIV. In a third case, however (Obs. XV.), the formula was different. This was a case of pleurisy which was being cured, but a day before we applied the vesicatory the patient was attacked by intense gastrointestinal disorders with hypothermia 95.7° F. (35.4° C.). This superadded affection sufficed to completely modify the cellular formula of the vesicatory fluid. This observation established the extreme sensitiveness of the procedure and shows with what rapidity pathologic influences affect the organic reactions.

TUBERCULOSIS.

	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.	X.	XI.	XII.	Pleurisies. XIII	XIV.	XV.
Neutrophilic polynuclears	9.26	85.5	95.0	96.0	91.6	98.6	95.00	89.25	62	90.0	92.6	74.10	71.4	66.3	91.0
Eosinophilic polynuclears	0	0	0.8	0	0	0	0	0	0	0.8	3.2	7.32	13.7	17.0	1.2
Large mononuclears	3.4	9.0	1.6	0	2.8	0.8	1.00	5.75	21	2.0	2.6	3.64	5.2	11.5	5.0
Small mononuclears	2.8	0	1.3	1.2	4.8	0	1.75	0	10	5.2	0.4	13.14	8.5	1.5	0
Neutrophilic myelocytes	0.8	3.5	0.3	0	0.8	0.6	0.75	1.5	7	0.4	0.8	0.18	0	1.2	1.8
Eosinophilic myelocytes	0	0	0	0	0	0	0	0	0	0	0.4	0.36	0	0.8	0.2
Vesicatory cells	0.4	2.0	1.0	2.8	0	0	1.5	3.5	0	1.6	0	0.76	1.2	1.7	0.4

I. Pulmonary tuberculosis at the third stage.

II. Pulmonary tuberculosis at the third stage.

III. Pulmonary tuberculosis at the third stage.

IV. Pulmonary tuberculosis at the second stage. Infiltration of the entire left lung.

V. Pulmonary tuberculosis in the second stage. Generalized bronchitis.

VI. Pulmonary tuberculosis in the second stage.

VII. Pulmonary tuberculosis in the second stage. Generalized bronchitis.

VIII. Pulmonary tuberculosis in the third stage. Intense fever.

IX. Pulmonary tuberculosis in the third stage. Hemoptyses. Fever. Erysipelas cured since twenty-six days. (Notice the small number of neutrophilic polynuclears and the large percentage of the mononuclears).

X. Tubercular pulmonary congestion.

XI. Pulmonary tuberculosis with fibrinous evolution. Tubercular peritonitis.

XII. Slight pulmonary tuberculosis. Dulness in the front and right side of the chest and the left side of the back; harsh respiration; a few dry râles and frictions. Apyrexia.

XIII. Acute serofibrinous pleurisy.

XIV. Acute serofibrinous pleurisy in a very vigorous man.

XV. Acute serofibrinous pleurisy on the way to recovery. Intense gastrointestinal disturbances and hypothermia since the previous day.

In erysipelas the eosinophiles, which are absent when the disease is at the stationary period, reappear at the moment of recovery. These elements, however, are few in number during the days immediately following the morbid termination. The organic reactions which are profoundly modified by the infectious attack, remain disturbed for a long time. At the same time that the percentage of the eosinophiles increases, that of the neutrophilic polynuclears diminishes at the end of the disease. The mononuclears are also far more numerous than at the stationary period.

We have employed the vesicatory test in two cases of mumps and one of acute angina. All these observations concur in demonstrating that the histological examination of the vesicatory fluid reveals the mode of reaction of the hematopoietic organs in a given case. In fact, we see that the same toxic cause, the application of cantharides, determines the presence of different cells in the vesicatory fluid according to the degree of intensity of the infectious impregnation, according as the organism resists with more or less success, and according to the phases of the struggle. This method is extremely sensitive. A superadded or even slight infection suffices to completely modify the results. It must, however be remembered that the vesicatory test indicates only the degree of intensity of infectious impregnation. An intense infection may be benign, for example, an acute angina. A slight infection may be more serious, even if the organism resists, for example, a local tuberculosis. The vesicatory test furnishes data concerning not the absolute prognosis of the infection, but the degree of impregnation of the organism. From a purely theoretical standpoint it is interesting to remark how an infection, though benign and well localized, modifies all the organic reactions. A catarrhal angina is sufficient to disturb the leucocytic equilibrium of the economy. Under these conditions the

same irritating cause produces other effects than in a normal individual. Our investigations thus explain why secondary infections so often differ in their mode of evolution from primary infections.

Diagnosis According to Chemical Modifications in Fluids. An infection produces not only histological but also chemical modifications in the blood and fluids. It causes notably the appearance in the serum and certain exudates of substances which seem to be intended to combat infection. Among these the most interesting from a diagnostic standpoint is that which causes agglutination of the microbes. Everyone is well acquainted with the practical application which Dr. Widal has made of this in the diagnosis of typhoid fever. The procedure is quite simple. A few drops of the blood of the patient are taken, and then the serum, diluted in a certain proportion, is mixed with a fresh culture of Eberth's typhoid bacillus. If the case is one of typhoid fever, the scattered elements unite in small masses. This method, designated as the "method of serum-diagnosis," is currently employed in the diagnosis of typhoid fever. According to the researches of Dr. Arloing and his disciples, this method is applicable also to tuberculosis. Other substances which are produced in the blood of infected subjects may likewise serve in diagnosis.

Among the secretions only one is commonly studied clinically, namely, the urine. Its examination in the course of infectious diseases is of great importance, but it is more interesting for prognosis than diagnosis. The modifications in quantity and color, the variations in the amount of cells and nitrogenous substances, the appearance of abnormal substances, such as albumin, peptones, and glucose, enable us to appreciate the changes occurring in the organs and in general nutrition, but do not help us to determine the nature of the disease. Likewise, the detection of biliary pigments—urobilin—is interesting only as regards prognosis. The only reaction which sometimes may serve for diagnostic purposes is Ehrlich's diazo reaction. Although it is not absolutely a specific, this reaction is an important sign in the diagnosis of typhoid fever. It is sometimes manifest as early as the third or fourth day, but may be delayed until the beginning of the second week. It also enables us to foretell certain complications. If it suddenly ceases unattended by concomitant amelioration, some secondary infection or a renal lesion must be suspected. If it increases in intensity it means an aggravation of the disease. Its reappearance during convalescence indicates

a relapse. The diazo reaction is likewise observed in typhus fever, in acute tuberculosis, pyemia, septicemia, measles, scarlatina, and at times in pneumonia.

Diagnosis by Therapeutics. We must now say a word regarding the influence of certain substances capable of modifying the evolution of affections and thus elucidating their character. Such are specific medicines, which serve to determine, as the case may be, the malarial or syphilitic nature of an infection. The action of quinine upon malaria is too well known to need more than an allusion. Syphilis has two specifics: salts of mercury and iodide of potassium. The test treatment is constantly employed in the diagnosis of difficult cases. It should be remembered, however, that the action of the iodides is exercised in the same manner in another infection, namely, actinomycosis. The specific character and diagnostic value of the iodides thus lose much of their importance. It is even likely that many cases of actinomycosis have been mistaken for instances of tertiary syphilis.

Diagnosis by Microbic Toxins. While the number of specifics drawn from the inorganic world are so small in number, it is hoped that microbic cultures will furnish some such specifics. This hope is founded upon the investigations of Koch. In studying the effects of tuberculin, this author showed that the reactions differ markedly according as this extract of cultures of tubercle bacilli is injected into a healthy or a tubercular individual. At the end of four to five hours after the injection a chill occurs, and the temperature rises as high as 102.2°, 104° F. and even higher, 105.8° F. (39°, 40° C. and even 41° C.). The patient feels tired. He is tortured by constant coughing, has at times nausea and vomiting. He experiences very intense pain in the epigastrium, extremities, and articulations. These symptoms last from twelve to fifteen hours; but may be prolonged for two or three days, or be followed by a secondary fever after the cessation of the reaction, depending upon infection by other microbes (pneumococci, staphylococci), the development of which is favored by the so-called "lymph." Coincidently with these general disturbances local phenomena in the tubercular lesions are produced, which may readily be appreciated by observing what occurs in the case of lupus. The diseased parts swell and become red. Here and there they become brown and necrosed. Two or three days later the redness diminishes and the lesion is covered with yellowish crusts formed by the air-dried serum. Two or three weeks later the crusts

become detached, and in favorable cases leave a cicatrix of good appearance. Several injections are generally required to obtain this result. In tuberculosis of the lymphatic glands, as well as in osseous and articular tuberculosis, the reactions are less intense, but they are always perceptible.

It was, therefore, hoped that the so-called "lymph" would serve to diagnose tuberculosis, and thus establish the nature of a suspicious lesion and also to decide whether an old focus was really cured. The specific value of tuberculin is notably diminished by the fact that it produces intense reactions in non-tubercular cases, for instance, in cases of cancer, syphilides, scarlatina, gonorrheal cystitis, leprosy, and actinomycosis. Several authors, and particularly Maydl, have observed a typical reaction in healthy individuals who had received only one or two milligrams of the "lymph." On the other hand, the injection does not always produce reactions in tuberculous subjects. Sometimes the general phenomena, and sometimes the local manifestations, are lacking. Furthermore, various substances, microbic or otherwise, may produce in tuberculous individuals disturbances similar to those caused by tuberculin. Injections of artificial serum are often followed by marked reactions, and, as is shown by Hutinel, these may be utilized for diagnosis. We may, therefore, conclude that Koch's "lymph" is not absolutely specific. Other substances behave in the same manner, and it does not act exclusively upon tubercular lesions. Nevertheless, some authors think that it may still be profitably employed at least in animals. German veterinarians who have studied its action upon tubercular cows have obtained reactions with doses of 3 to 10 centigrams, which produce no disturbance whatever in healthy cows.

Mallein. The discovery of tuberculin by Koch led bacteriologists to search for analogous substances in other cultures. Thus Helman and Kalning prepared a substance designated mallein, which has been the subject of numerous investigations, especially by Preusse, Pearson, Foth, Babes, Nocard, and Bonome.

Inoculation of mallein into animals suffering from glanders produces at the injected point a hot, painful tumefaction which increases for twenty-four or thirty-six hours, and disappears in eight or ten days. Synchronously the general state is modified. There is prostration; the animal looks depressed, anxious; its breathing is accelerated, and it may have chills and convulsions. A febrile movement finally sets in which reaches its maximum after ten or twelve

hours, seldom later. The rise in temperature amounts to 2.7° to 4.5° F. (1.5° to 2.5° C.). It is to be noted that the mallein test is conclusive only in those cases in which the inoculation is made upon animals having previously been at rest for forty-eight hours and protected, after inoculation, against atmospheric variations.

If reaction is clear—*i. e.*, if the thermal elevation is regularly produced and reaches 2.7° F. (1.5° C.), the existence of glanders may be affirmed with a fair degree of assurance. If the temperature is raised 3.6° F. (2° C.), diagnosis is positive, and the animal is killed. When reaction is incomplete or irregular the animal is left at rest for four to six weeks, and then the experiment is resumed with little larger doses.

The employment of mallein has rendered immense service. By revealing with a fair degree of certainty the existence of glanders and treat it from the very beginning, mallein will certainly serve to decrease and finally extinguish this disease. The mallein test may also be applied to man, provided small doses are employed. It has thus been injected with success by Bonome and by Buscke.

Recapitulation. The foregoing various scientific procedures of diagnosis, which are mostly drawn from recent bacteriological discoveries, may render immense service to the nosologist by enabling him to give a solid basis to clinical observations; but they are of less importance in practice. In spite of their apparent simplicity, they require a vast amount of technical experience, and the positive character of laboratory researches renders possible quite harmful errors. It should not, therefore, be imagined, as is too often done, that bacteriology will furnish the physician with simple and certain procedures. The difficulties, although of a different character, exist none the less. Even supposing that the practitioner has acquired sufficient skill to utilize the modern methods of investigation, it must be remembered that bacteriology is incapable of solving all the problems which confront the physician in connection with each particular case observed. When he recognizes that the disturbances are due to a definite microbe he will not have finished his task. A complete diagnosis must answer many other questions. For example, a patient whose expectorations contain the pneumococcus, and whose respiratory apparatus is the seat of a lesion dependent upon this microbe, may have a bronchitis, or a capillary bronchitis, or a bronchopneumonia, or a fibrinous pneumonia. The same microbe is concerned in all four instances; but the affection pro-

duced is quite different from the quadruple standpoint of anatomico-pathological localization, evolution, prognosis, and treatment. It may be answered that the nature of the morbid reaction is not of prime importance, and that the point to be decided is the nature of the pathogenic agent. As soon as this is done the specific treatment can be applied and the evolution of the disease arrested. For the present, however, this is a dangerous utopia. Even in the case of diphtheria, the only infection for which we possess a specific, the physician will be bitterly disappointed if he fancies that it suffices to inject antitoxin as soon as the bacillus is discovered. On the contrary, he must establish a complete diagnosis, determine the state and extent of the lesions, and learn under what conditions these develop and in what kind of soil they evolve.

Rules of Clinical Diagnosis. It is evident that the questions which must be solved in the presence of a patient apparently suffering from an infection vary from one case to another. They may, nevertheless, be grouped in the following manner:

1. What are the present disturbances? The sensations felt by the patient, the objective phenomena which he presents enable the physician to answer this first question. He may thus lay down the symptoms which he observes.

2. What is the immediate cause of these disturbances, namely, with what organs or systems are they to be associated? This second question is more difficult. In fact, symptoms are divided into two groups. Some of them express the suffering of an organ and immediately draw the attention of the physician to this organ. Cough or dyspnea leads him to auscultate the lungs. Palpitation of the heart leads him to examine the heart, and impotence of the lower extremities leads him to study the nervous system. If, however, he weighs the close synergies connecting the various parts of the organism he will remember that the disorders of these organs may depend upon some other organ. Thus we arrive at the third question.

3. Are the suffering parts primarily or secondarily affected? Are their disorders or lesions independent or due to the same cause? Among the organs affected, in which one did the disorders upon which the other symptoms depend first become manifest?

All these questions may be solved only in one way. The physician must examine systematically the various parts of the organism, those which seem to be diseased as well as those which appear healthy.

4. The succession of the present symptoms having been established, the physician must solve the question whether the present affection is the result of a previous disease or whether it is a primary malady.

5. In the latter instance he must investigate the nature of this disease and its place in nosology. It is here, and here only, that modern procedures intervene, and bacteriology, at least in certain cases, may profitably be resorted to. However, even when a search for the microbe enables the physician to assign to the disease its true place in nosology, his task is not yet completed. He has a last and, perhaps, the most important question to solve, for the diagnosis and part of the treatment depend upon it, namely:

6. In what soil is the disease evolving? What clinical form does it assume? What organs are secondarily involved? Having made a complete examination of the patient, the physician, in most cases, finds sufficient data to answer the questions connected with the diagnosis. Although he cannot always reach definite conclusions, he can at least make a more or less close approach to accuracy. At the beginning of the disease he may remain in doubt, but he hesitates only between two or three hypotheses, and, in general, after a day or two the evolution of the disease, by modifying the clinical aspect, leads him to an exact and definitive conception of the events. Thus, for example, he is called to decide the case of a child or a young man suddenly attacked by angina. He finds fever, a rapid pulse, a coated tongue, and a red throat with some yellowish exudate upon the tonsils. The diagnosis of acute angina is evident, but what is the nature of this angina? This is more difficult to determine, and yet the question is of prime importance from a prognostic and therapeutic standpoint. The sudden onset, the pultaceous aspect of the tonsillar deposit, and the frankly inflammatory reaction lead the physician to eliminate diphtheria. But is the case one of simple angina or of a scarlatinal angina? The age of the subject, intensity of the fever, the intense redness of the throat, the rapidity of the pulse, and at times the existence of a concomitant epidemic, cause the physician to incline to a diagnosis of scarlatina. A final decision is impossible, however. He must wait for the appearance of the eruption, that is, until the third day of the disease, in order to definitely decide the question. In this instance, a symptomatic manifestation of prime importance in diagnosis is lacking.

In other cases an exact diagnosis, which seems to be justified by no symptom, may be laid down from the very beginning. Thus a child eight or ten years of age is suddenly taken by intense fever. It suffers from dyspnea and a very irritating dry cough. The face is congested, the cheeks red, and the temperature at 104° F. (40° C.). Although auscultation gives negative results, the physician diagnoses pneumonia, and, in reality, after twenty-four hours, sometimes after two or three days, the characteristic bronchial murmur is heard. Owing to a little practice the diagnosis was made at the outset in spite of the absence of stethoscopic signs and in spite of the presence, in certain instances, of nervous phenomena and even convulsions, which might first lead to a diagnosis of meningitis.

It would be easy to multiply illustrations. These few suffice to establish that, in most infections, diagnosis may be made if the whole organism is systematically and minutely examined.

When the physician has recognized the nature of the disease he has not yet completed his task. Let us suppose the case of a man who has been suddenly taken by a chill, followed by pain in the side, an irritating cough, brick-dust expectoration, and intense fever. On auscultation we find in one of the lungs a focus of crepitant râles or tubal murmur. The state of the lung explains all the disorders, and the evolution of the disease enables us to state that we are dealing with an infection—*i. e.*, pneumonia. We have thus answered all the questions which we had to solve, except the last one. It was easy to make the diagnosis of pneumonia in this instance.

It is more difficult to determine in what soil the infection evolves. In this connection it is important carefully to interrogate the patient as regards his hereditary as well as personal morbid antecedents. In this connection, also, all the viscera must be carefully examined. The physician does well to auscultate the lungs in order to recognize the disease; but he must never be contented with so summary a diagnosis. The prognosis and the treatment are to be based upon the knowledge he acquires of the previous condition of the subject and the present state of the various organs. Then, and then only, will he reach a complete diagnosis and be able to foretell the evolution of the disease. If pneumonia develops in a young and vigorous individual, recovery is the rule. If it occurs in an aged person, the termination is in most cases fatal. In both of these instances pathology seems to furnish sufficient information. Let us now

consider an apparently vigorous patient attacked by pneumonia. One might believe that he will recover without much hinderance. On making a systematic examination of his organs and an analysis of the urine a lesion until then latent is discovered, a cardiac affection, a sclerosis, or else albuminuria, or glycosuria, or, lastly, there are found secondary localizations in other organs, endocarditis or myocarditis. The evolution will then be different. An exact conception of the disease is obtained by careful examination of the entire organism.

The example which we have chosen was a simple one. At any rate, it may be said that it is relatively easy to diagnose an infectious disease. The physician has to deal with a recent acute evolution, all the phases of which are observable, since he is examining the case at a stage quite near the beginning of the evolution. In most cases, in order to arrive at a diagnosis, it suffices to have studied pathology well. The only important point is to make a complete diagnosis, for, as we have often repeated, the manifestations are far more diffuse than is at first believed. The microbic toxins affect the whole economy, and the duty of the clinician is to learn what parts are affected and in what degree they are involved. To find the designation under which the infection is to be classed is a relatively easy task; but diagnosis, however exact it may appear to be, is incomplete and insufficient, and answers only the first, the easiest and the least important part of the problem.

In order to facilitate the task of the physician, nosologists have admitted a certain number of clinical forms in infectious diseases. Taking typhoid fever and pneumonia as examples, we have shown how it is possible, by considering either the state of the subject or the general disturbances or the localizations, to classify the various types and furnish precise indications for the guidance of the physician. These forms, however numerous they may be, do not, of course, respond to all the clinical varieties and their innumerable variations; but they may supply valuable data, and must, therefore, be most carefully studied. In certain instances the complexity of the clinical form is due to the coexistence of various manifestations or multiple localizations. It is, therefore, very difficult at times to connect them with each other. Thus, we may have to deal with a case of erysipelas in which, at a given moment, a pulmonary murmur is detected. Is the process a streptococcic infection—*i. e.*, a visceral localization dependent upon the agent which has caused the first

disease? or is it an infection due to a superadded microbe, the pneumococcus? Both varieties of pneumonia have been observed in erysipelas, and, without bacteriological examination of the sputa, it is generally impossible to make the diagnosis.

The difficulty is still greater when the pathogenic agents are unknown. In an individual presenting a scarlatiniform eruption coincident with other infectious manifestations, how can we affirm whether the case is one of erythema or a true scarlatina? It would be equally right to hesitate in certain cases in which multiple articular symptoms occur in scarlatinal patients at the period of convalescence. Do they depend upon scarlatina or a concomitant acute articular rheumatism? Not infrequently the physician remains in doubt with regard to all these questions. In order to classify and interpret the disturbances, the physician does not need, as is often stated, a particular talent, a sort of divining gift. The skill of making a diagnosis is not inborn. On the contrary, it is acquired by theoretical and practical study of pathology and by repeated examination of patients. As a matter of fact, we see in clinics cases far more complex than the study of pathology makes us believe. Didactic studies give only schematic descriptions. They consider diseases in their fundamental and constant characters, regardless of the soil in which they run their course. It is precisely because this soil is so eminently variable that clinical types are so numerous and varied. The duty of the physician is, therefore, to determine the soil in which the disease evolves, and from this determination he must draw the greater part of his knowledge of its ulterior evolution.

After the physician has succeeded in discovering the present state of the patient, his resistance, his reactionary aptitudes, the functional activity and alterations of his organs, he will be in a position to predict the evolution of the process he observes. To answer this last question is to establish a prognosis, that is, to solve the most difficult and important problem in medical art.

Prognosis.

It is evident that, in the matter of prognosis, the nature of the disease is first to be considered. Certain infections almost always terminate fatally, and others end in recovery. In such cases prognosis is drawn simply from diagnosis. Tubercular meningitis, acute

mania, and hydrophobia are always or nearly always fatal. On the other hand, varicella, mumps, herpetic anginas, and simple pneumonia in children always or nearly always end in recovery. Nothing seems to be simpler. Even in these cases, however, there are exceptions. Varicella at times proves fatal, and a good number of distinguished physicians assert that tubercular meningitis is curable. These exceptions, one may say, should not be taken into account. Let us, therefore, set aside these facts and consider the most frequent cases. When we have to deal with an infection with variable prognosis, whence shall we draw our data of appreciation? We may first resort to statistics. From this point of view I have looked up the observations in our wards during the last five years. These observations are 8832 in number, comprising 602 fatal cases, that is, a proportion of 6.8 per cent. From tabulation of these figures we may draw certain important conclusions with reference to prognosis. In fact, it will not suffice to consider the results in a general way. Although it is interesting to know what the general mortality is in each disease, it is indispensable to push analysis a little further. Here are some conclusions regarding the influence of age and sex upon prognosis:

Influence of Age. It may broadly be stated that mortality is very high during infancy and is considerably reduced after two years of age. In the adult, according to the disease under consideration, mortality may be greater or less than that in second childhood. Thus, in measles, scarlatina, varicella, diphtheria, and anginas the mortality in adults is far below that in children. Such is not the case with erysipelas. The mortality, which is 45 per cent. before two years, falls to 0 between two and fourteen years of age. Between fifteen and thirty years it hardly exceeds 1 per cent.; then it rises with age. It oscillates around 4 or 5 per cent. from thirty-one to fifty years of age. It may be remarked that, during infancy, erysipelas kills of itself by streptococcic generalization. In the adult, on the contrary, death commonly results from a complication or a previous organic lesion which has weakened the resistance. The influence of age is no less important in other diseases, especially in measles. During infancy the mortality reaches 27.7 per cent It falls to 6.6 per cent. in childhood, and to 0.8 per cent. in adults. Three principal factors explain the higher percentage in young children, namely, bronchopneumonia, tuberculosis, and suppurations and gangrenes. The influence of measles upon the course of

tuberculosis has long been noted. The younger the subject the more marked is the action of this eruptive fever upon the evolution of tuberculosis. Bronchopneumonia, suppurations, and gangrenes depend upon common germs, which are closely allied to each other, and upon pus-cocci. Young children are particularly predisposed to the action of these bacteria, but they run the risk of infection especially when they are placed under bad hygienic conditions. The frequency and gravity of superadded pyogenic infections in young children are likewise proved by the study of other diseases. Scarlatina, which has little tendency to affect the respiratory organs, may kill at this age by bronchopneumonia. Finally, varicella, which is too often considered as a mild disease, gives a mortality of more than 7 per cent.

Influence of Sex. The influence of sex, which is *nil* during childhood, varies in adult age according to the disease under consideration. According to our statistics, mortality is the same in both sexes for scarlatina, somewhat higher in men in measles and especially in variola. For the latter infection, the mortality is 26.2 per cent. in men, and 22.1 per cent in women. The differences are analogous in erysipelas. In this affection the mortality is 5.99 per cent. in men, and 3.67 per cent. in women. I believe that the higher percentage of mortality in males is due to the influence of alcohol. Chronic intoxication by alcohol causes nutritional disturbances and visceral lesions which lend a particularly serious character to infections. In measles and scarlatina mortality is nearly the same in both sexes, because the individuals attacked are still very young and are not yet sufficiently impregnated with alcohol. Variola and erysipelas are often observed in individuals more advanced in age, and, therefore, the mortality in men is higher than in women.

This is the information that may be drawn from the statistics. In spite of their interest they are insufficient to assist materially in diagnosis. Therefore, in order to foretell the probable evolution of a disease it is necessary to consider the data of another order.

Influence of Epidemics. The elements which serve as a basis for prognosis may be divided into two groups. On the one hand, the characters of the disease must be considered, viz., the conditions under which it is developed, the symptoms it presents, and the course it follows. Next, the soil in which the disease evolves is to be studied. The first information is furnished by epidemiology. It is known that at certain moments diseases become aggravated or

attenuated. We often notice changes in the evolution of influenza, pneumonia, and typhoid fever. For a few years past diphtheria was very benign. At present it seems to assume a more serious character. The same remark may be made with regard to scarlatina. Moreover, it is known that in the course of the same epidemic the gravity follows a course nearly parallel to that of morbidity. Benign cases are frequent at the end of the epidemic. The hygienic conditions under which a patient is placed should also be taken into consideration, whether he is being treated in a hospital or at home. These are evident truths upon which it is useless to dwell.

Importance of Etiological Conditions. Certain importance is often attached to the knowledge of the etiological conditions. It has been demonstrated, however, by a great many examples that a disease contracted from a profoundly infected individual may prove to be benign, and *vice versa*. In this connection, nothing is more instructive than the study of venereal infections. In many cases in which these affections have been transmitted to several individuals under etiological conditions as similar as possible, the evolution in the various subjects has been quite different. In certain cases, however, an exalted virus produces, by contagion, grave diseases. To be convinced of this, it will suffice to state what occurs with regard to pneumonia in certain family epidemics. By thus following the course of these infections successively contracted we may often see the process become more and more serious as it spreads. The person first attacked has a benign infection, which assumes a progressively graver character as it is transmitted to persons about him. Analogous observations have been made by Dr. Quelmé with regard to dysentery in Bretagne.

In the case of an inoculated infection prognosis depends partly upon the mode of entrance of the virus. The gravity of extragenital syphilis has long been known. A better example is furnished by hydrophobia. Not to speak of cases in which bites inflicted upon parts protected by clothing produce no symptoms, statistics show that wounds of the fingers and face are particularly serious, because these regions are rich in nervous terminations. The mortality is about 87 per cent. for bites of the face, 66 per cent. for those of the hands, 29 per cent. for those of the upper extremities, and 19 per cent. only for those of the lower. Finally, it may be stated that in the case of infections which may be transmitted by several pro-

cedures prognosis is least serious in accidental inoculation. Glanders produced by subcutaneous inoculation is quite often cured. It is likewise known that the prognosis of anatomical tubercles—*i.e.*, contracted at necropsy—is generally favorable.

Importance of the Duration of Incubation and of the Mode of Invasion. When the moment in which the infection has occurred can be determined, it is possible to draw some information from the length of incubation. We have already noticed that the period of incubation is abridged under two quite different circumstances, namely, when the virus is very active and, consequently, the prognosis is evidently grave, or when the organism is capable of very energetic reaction and the incubation is short and of favorable significance. The difference will be appreciated in view of the concomitant circumstances.

The same remarks are applicable to the mode of invasion. With a very sudden and tumultuous onset, an infection may be very benign and even very short. Therefore, to exactly appreciate the importance of the mode of onset, we must consider the accompanying phenomena. If these are not very intense this suddenness of the initial manifestations indicates a favorable evolution. If they are intense, a grave, or at least a serious, form may be predicted. In certain instances the knowledge of the initial manifestations may serve in diagnosis. Thus, surgeons have established an important difference between phlegmons which begin with local phenomena and those attended from the first by general reactions. In the latter instance the profounder impregnation of the organism is connected with a greater gravity of the process.

A relationship is generally believed to exist between the duration of invasion and the gravity of a disease. This the author does not believe to be true except with respect to variola. In this infection a short invasion, not exceeding two days or two and a half days, is a sign of confluent variola. An invasion lasting three or four days indicates a discrete variola. It is true that an eruption beginning after four full days is seldom confluent. This, however, is acceptable with some reservation.

Bases of Prognosis at the Stationary Period. As a rule, when a disease has reached the stationary period the physician possesses all the necessary elements for prognosis. These elements are four in number: First, the local lesion or the principal expression of the infection—the eruption in cases of eruptive fevers. Second, the

state of the parts surrounding the local lesion. Third, the general phenomena. Fourth, the condition of the principal organs.

Let us immediately remark that if an analytical examination is necessary, the prognosis must be established in view of the ensemble of the researches above indicated. To determine the extent of the local lesion or the intensity of the general phenomena does not suffice. These two orders of manifestations must be compared in order to draw a conclusion It may broadly be stated that prognosis is grave in proportion as the local lesion is intense and especially extensive. This is true as regards pneumonia as well as erysipelas and the eruptive fevers, and particularly so with respect to variola. The prognosis of the latter disease depends entirely upon the character of the eruption. Of course, the study of the general phenomena is important, but that of the cutaneous manifestations is still more important. The condition of the parts surrounding the local lesion must, as a rule, be taken into consideration. In the case of pneumonia and tuberculosis the information furnished by the examination of the portions of parenchyma spared by the principal process is of considerable importance. The phenomena of congestion or edema which may take place therein greatly affect the prognosis.

As already stated the conditions of the local lesion and of the general state must be compared. Violent general reactions are much less grave than adynamic manifestations.

Finally, the examination must be completed by determining the condition of the organs, heart, lungs, and liver, and by analyzing the urine. Thus information is obtained concerning the function of and the possible complications occurring in the viscera. This complementary examination shows the influence of the present infection upon the principal organs, and thus enables us to form an idea of the previous condition and pre-existing lesions of the organs. In this manner we obtain valuable indications for prognosis, for it is not sufficient to determine the characters of the present disease, its intensity, and the lesions which it produces or complications to which it gives rise. We must know the soil in which the disease evolves in order to establish the prognosis.

We hardly need dwell upon the importance of the general state of the individual at the time when he is attacked by an intercurrent disease. We know the gravity of an infection attacking a cachectic, emaciated individual having suffered privations, exposure, overwork, and excessive fatigue. In all debilitated individuals evolution is

grave, and the defensive reactions being often nearly impossible, a fatal termination soon takes place. Fatigue and overwork not only render prognosis unfavorable by aggravating the course of the disease, but also by favoring certain morbid localizations. We have already referred to the frequency of myocarditis in overworked individuals. In certain cases the cardiac infection ends in the formation of an abscess. In other instances overexertion gives rise to cerebral localizations. It will suffice to recall the frequency of delirium under these conditions. We have a more palpable illustration in cerebral rheumatism, a grave manifestation which is observed only among a certain class of individuals.

Nutritional disturbances dependent upon a diathetic state likewise exercise an unfavorable influence upon the course of infections. The gravity of infections in the obese may be cited as an example of this. The very thick adipose tissue seems to prevent the dissipation of heat in fever. On the other hand, the disorders of nutrition engendered by obesity render the reactions sluggish and less energetic. Hence, after the termination of the disease its effects are prolonged beyond the usual limits. The ill-nourished skin is easily invaded by external germs. Not infrequently furuncles, anthrax, and especially sloughs occur, particularly in the sacral region.

Among the diseases connected with disturbances of nutrition we may cite gout and diabetes. In this connection gout is of little importance. We have observed several cases of erysipelas in gouty individuals in whom the evolution terminated in a favorable manner. The rôle of diabetes is more important. It is known that this disease predisposes to cutaneous infections, pulmonary inflammations and tuberculosis. It imparts to these processes a particularly rapid and grave evolution. Infections of the skin and lungs are easily complicated with gangrene. In other cases pneumonia assumes a galloping course. The gravity of infections should not, however, be exaggerated as regards diabetic patients. We have seen several such patients attacked by erysipelas, and all recovered. It is true that the infection was particularly intense, attended by delirium, and prolonged beyond the average duration.

Another element of prognosis is drawn from the knowledge of previous infections and especially intoxications of the individual. With reference to relapsing infections it has been asserted that successive attacks gradually lose their intensity. This law does not seem to the author quite true. It is not true with regard to erysipelas, and

many cases are on record in which individuals have succumbed to a second or third attack of variola.

In treating of microbic associations we have shown the rôle of previous or concomitant infections and emphasized the fact that results varied according to the case under observation. It may be recalled that erysipelas occurring during convalescence from scarlatina is very benign, while pneumonia supervening in the course of erysipelas is always highly dangerous. It is evident that a preexisting chronic infection aggravates the prognosis of an intercurrent infection. This is true as regards syphilis, malaria, and especially tuberculosis. Furthermore, intercurrent disease may awaken a previous infection, bring about a recurrence of malarial paroxysms, and impart to a chronic tuberculosis an acute course.

Previous intoxications likewise modify prognosis. Owing to disturbances of nutrition and the organic lesions to which they give rise, they aggravate infections. Alcoholism is to be considered in a particular manner in this connection. It is not so much by questioning the patient as by analysis of the phenomena observed, and particularly cerebral symptoms, that the physician recognizes this intoxication. We may repeat, however, that alcohol acts not only upon the nervous system, but causes important lesions in the viscera and particularly in the liver. We are thus led to investigate the rôle of visceral affections upon the course of infections and their importance from a prognostic standpoint.

Role of Previous Visceropathies. As has already been stated, the lesions of the heart do not markedly aggravate the prognosis. Contrary to what might be supposed, a chronic endocarditis seldom forms the focus for a new cardiac localization. The prognosis depends, not upon the extent or the nature of the valvular lesion, but upon the condition of the cardiac muscle and the influence which its disorders may have exerted upon various organs. Hence, chronic myocarditis renders prognosis more unfavorable than an aortic or mitral lesion.

Lesions of the lungs, aside from tuberculosis, may, when they disturb hematosis, hinder oxidation. They have also the inconvenience of disturbing the action of certain therapeutic methods. Baths, even when lukewarm, are very badly borne by emphysematous subjects. Finally, when pulmonary lesions influence the heart, they produce through this organ visceral disturbances the importance of which we are about to consider.

Lesions of the kidneys notwithstanding that they hinder organic depuration, do not render prognosis very unfavorable. No doubt we often see a Bright's patient succumb to an infectious complication, suppuration, erysipelas, or pneumonia; but this is at the last period. When the individual is still resistant he endures well an intercurrent infection, notably erysipelas. Lesions of the liver are of greater consequence, but we must make an important distinction analogous to that which we have admitted with reference to the heart. It is not the extent or the topography of the sclerotic lesions, but the condition of the hepatic cells that is to be considered. A hypertrophic biliary sclerosis does not prevent the favorable evolution of erysipelas; an atrophic sclerosis renders the prognosis quite serious The same is true of diffuse steatosis of the liver, as may be observed in alcoholic individuals. The lesion of the cells explains the development of nervous accidents, notably delirium tremens, and accounts for the fatal termination. It is well to bear in mind, however, that hepatic lesions, even when extensive, sometimes remain latent. On the occasion of an intercurrent infection symptoms of hepatic insufficiency may become manifest. Affections of the stomach and intestine may favor or hinder various infectious lesions. Hence, the great service of gastrointestinal antisepsis in the therapeutics of the most varied infections. It may also be stated that predisposition plays a very important rôle in the development of grave nervous manifestations, and thus accounts for the persistence or the appearance of certain disorders which may persist after recovery.

General Rules of Prognosis. It is evidently impossible to lay down general rules of prognosis. We have mentioned the principal questions which the clinician has to solve. We may explain the method by an example. Let us suppose that we are dealing with a case of pneumonia. Examination of the lungs is of prime importance for diagnosis, but not so for prognosis. It is undoubtedly interesting to know the extent of the hepatized zone, which may be judged by the extent of the tubal murmur; but a more important element to be considered is the condition of the parts surrounding the morbid focus and the extent and intensity of concomitant congestion. The other organs are to be considered more than the lungs. Examination of the urine, of the liver, and especially of the heart, is of chief importance in the diagnosis. An excessive acceleration of the heartbeats, their weakness, and the appearance of fetal rhythm must guide both prognosis and therapeutics. Moreover, we must determine the

constitutional ground upon which this pneumonia evolves, because, with the same lesion and with the same influence of the lesion upon the other organs the prognosis differs according as the case is that of a young or old, robust or debilitated, temperate or alcoholic individual.

When all these problems have been solved the task of the physician is not yet over. Prognosis must answer the following three questions: 1. What will be the termination of the present disease? 2. What is its bearing upon the future of the patient? 3. Of what importance is it for his descendants? It should, therefore, be determined whether the disease will be cured without leaving any appreciable traces and whether some disturbances will persist in consequence. It should be decided whether relapses or recurrences are apt to take place, and whether they can possibly be guarded against. It should also be predicted whether there will be any sequelæ in the remote future, or whether the descendants of the patient will be liable to degeneration or sickness. Along with the prognosis of the individual the prognosis of the race must be laid down. Then, and then only, has the physician answered all the questions which incessantly meet him on confronting each patient.

In establishing the rules of prognosis we have depended upon quite simple clinical procedures. As a matter of fact, laboratory procedures are in this respect of little importance. It was for a time believed that bacteriology would supplant clinical observation. The study of diphtheria led to the erroneous conclusion that examination of cultures enabled one to determine the gravity of angina, even in the absence of clinical observation of the patient. If the diphtheria was found to be uncomplicated, and if the bacillus developed upon the serum medium was not too long, the prognosis was favorable. If, on the contrary, the bacillus was long and mixed with numerous streptococci, the prognosis was grave. Although such correspondence may at times be observed, it is far from being the rule, and cannot replace examination of the sick or even modify the prognosis based upon clinical observation. We likewise believe that no practical information can be derived from inoculations into animals. Apart from the difficulties of the method, the results are too variable to be taken as a basis of prognosis. A microbe virulent for man not infrequently proves inoffensive for animals, and *vice versa*. Finally, P. Courmont has recently proposed an ingenious method of serum prognosis based upon the intensity of the agglutinating reaction.

This method is evidently very interesting and perfectly rational, since it is founded upon the appreciation of the organic reactions against the infection, but it has thus far been applied to typhoid fever alone, and while it may render some service, it is, like all other laboratory procedures, too complex and delicate to enter into current practice.

We, therefore, conclude that prognosis even more than diagnosis should be based upon simple procedures, upon an attentive examination of the patient, and minute and complete analysis of the disturbances which he presents. As for diagnosis, so for prognosis: It is not by a sort of divining power that the physician succeeds in solving the problems presenting themselves with each case, but simply by a profound study of pathology and long clinical experience.

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CHAPTER XXII.

THERAPEUTICS OF INFECTIOUS DISEASES.

General Considerations on the Therapeutics of Infections. Toxic and Therapeutic Equivalents of Medicines. Action of Medicines upon Normal and Infected Individuals. Principal Therapeutic Methods Employed in Infections. Antiseptic Method. Physical Agents. Chemical Antiseptics. Determination of the Antiseptic Power of Medicines. Choice of Antiseptics. Antisepsis of the Skin. Antisepsis of the Genital and Urinary Organs. Antisepsis of the Mouth and Nose. Treatment of Purulent Rhinites. Antisepsis of the Respiratory Passages. Antisepsis of the Alimentary Canal. Importance of Insoluble Antiseptics. Antisepsis of Serous Membranes. Intestinal Antisepsis. Employment of Peroxide of Hydrogen. General Antisepsis. Antitoxinic Method. Specific Medication: Cinchona, Mercury, Iodine, and Salicylic Acid. Bacteriotherapy. Employment of Sterilized Cultures of Streptococcus and B. prodigiosus. Attempts in Cancer and Lupus. Tuberculin. Mallein. Serumtherapy. General Principles. Various Applications of Serumtherapy. Serumtherapy against Cholera, Colon Bacillus, Diphtheria, Leprosy, Glanders, Bubonic Plague, Pneumococcosis, Proteobacillosis, Pyocyanobacillosis, Staphylococcosis, Streptococcosis, Puerperal Fever, Tetanus, Tuberculosis, Typhoid Fever, Eruptive Fevers, Vaccinia, Variola, and Hydrophobia. Prophylactic Injections of Serum. Accidents Ascribable to Serumtherapy: Cutaneous and Articular Manifestations; Fever; Albuminuria, Hemorrhages, and Nutritional Disturbances. Post-serum Therapic Hysteria. Prognosis of Serumtherapic Accidents. Mode of Action of Therapeutic Serums. Conclusions.

By their natural evolution, acute infections tend toward recovery. The duty of the physician is to observe the procedures resorted to by nature, and, thus inspired, to direct the morbid reactions and stimulate or restrain them, as the case may be.

The organism endeavors to destroy and expel infectious germs and to neutralize and eliminate toxins. Similarly our therapeutic measures should be directed to the accomplishment of these four purposes. Various procedures which not infrequently differ from those employed by nature may, however, be utilized in therapeutics.

To combat the animate agent which gives rise to infection is to practise etiological medication. To deal with the toxins through which the morbific germ acts is to practise pathogenic or physiological therapeutics, as the case may be.

Etiological medication is the application of the old adage: *Sublata causa effectus tollitur.* It finds its formula in the antiseptic method. The ideal would be the possession of substances which would destroy

the germs and be inoffensive for the patient. Unfortunately, here is the stumbling-block. Nevertheless, it is possible, with certain precautions, to realize antisepsis in surface wounds and at times in fistulous tracts. Even in wounds, certain antiseptics exert an irritant action. They diminish the resistance of the cells, and, in spite of their incontestable action upon the microbe, they favor rather than hinder infection. At present, therefore, the tendency is to substitute asepsis for antisepsis, and, when antiseptic substances are employed, care is taken to use weak solutions. With these precautions the results are often satisfactory, provided, however, the antiseptics are frequently changed. When any one of them is used for a long period of time, the action is weakened through habit.

The abortive method, which is calculated to arrest an infection at its beginning, belongs to the antiseptic method, and it is probable that specific medication should also be included in the same group.

We are acquainted with certain substances which arrest the course of certain infections. It is hardly necessary to mention the action of quinine in malaria, of mercury and the iodides in syphilis, and of the salicylates in rheumatism. The germicidal serums also belong to this group. They represent the specific antiseptics par excellence, possessing a selective action in destroying certain microbes and being powerless against allied germs.

The microbe, as we have repeatedly stated, is not the sole cause of an infectious disease. Auxiliary and predisposing causes often come to its assistance. The therapeutist must take them into consideration. His method is equally etiological when he struggles against the various conditions which favor, maintain, or aggravate infection. He can fulfil therapeutic indications by means of diet, hygiene, and at times through special medication or surgical intervention. Furunculosis may be cured by combating the digestive disturbances which produce or sustain it; suppuration may be arrested by extirpating the foreign body which is found in the morbid focus. While in these cases medication is not directed against the primary cause, it none the less deserves to be considered as etiological medication.

Pathogenic medication is that which combats the harmful action of the pathogenic agent upon the organism. Bacteria act mainly by their toxins. Therefore, all treatment directed against bacterial poisons we consider as pathogenic. In many cases, however, pathogenic treatment is confounded with physiological or naturalistic

treatment, which is intended to act against toxins, following the processes which the organism employs for the same purpose. The distinction is in fact of little importance, for it may be said that the struggle against infections conducted by the organism is carried on on lines of pathogenic therapeutics. In support of this assertion it will suffice to cite serumtherapy. We have stated above that certain germicidal serums which destroy microbes, or at least exert upon them a harmful action, represent an etiological method of treatment. The serums which neutralize the effect of toxins are more important. When we employ them against an infection, when, for instance, we inject antidiphtheritic serum into a patient, we practise pathogenic as well as naturalistic therapeutics—pathogenic, because we combat the mode of action of the cause; naturalistic, because we are guided by the reactionary mode of the diseased organism. In fact, we know that, in order to combat the microbic poison, the organism secretes an antitoxin. Through the agency of therapeutics we furnish to the organism, from the very start of the disease, the protective substance which it needs. We realize sooner what the organism would realize later. Thus we save time by arresting bacterial intoxication at a moment when its effects are still reparable.

It is not the bacterial poisons alone, however, that are to be reckoned with in infections. The synergy which unites all the parts of the organism spreads the disturbances throughout the entire economy. Hence the secondary autointoxications, which should never be lost sight of. In many cases procedures directed against these poisons are nearly the same as those employed against toxins. In fact, an attempt may be made to neutralize the noxious substances formed by the organism or to stimulate the organs charged with the function of destroying them, or an effort may be made to favor their elimination.

In order to neutralize the autogenic poisons the oxidizing method, which seems to act upon the microbic as well as upon the animal toxins, is generally employed. When it is desired to stimulate the organs concerned in the destruction of poisons, use should be made of various substances capable of stimulating the cells, notably those of the liver. The rôle played by alimentation has already been referred to. It will suffice to add that ether, in small doses, exerts a very manifest action upon this gland.

The liver acts upon animal and certain microbic toxins, and, in addition, possesses the power of destroying a great number of bac-

teria. Thus the many indications to which this therapeutic method responds are evident.

The same complexity in effects appears with regard to elimination. The simplest procedure seems to be represented by blood-letting. The flow of the blood carries away a certain amount of toxins. In reality, however, the action of blood-letting is very complex, because, at the same time that the constitution of the blood is modified, the exchanges are stimulated and the work of the heart is diminished. Blood-letting does not, therefore, represent a simple antitoxic method.

The elimination of toxins and, coincidently, microbes may likewise be favored by stimulating the emunctories, the digestive tract, the skin, and, particularly, the kidneys. Lavage of the stomach and intestine, the administration of emetics and purgatives serve to carry away the noxious elements which originate in the alimentary canal or are thrown into it. Certain drugs may increase the activity of the emunctories. Sudorifics, diuretics, and tepid beverages are often employed. In the treatment of acute infections, however, physical procedures are generally preferred. Heat or cold are called into play, as the case may be. Dry heat favors sweating. Moist heat stimulates or quiets the nerves. Lastly, a cold bath acts not so much by dissipating the heat of the body as by modifying the dynamic state of the organism by means of the nervous reactions to which it gives rise. It acts upon the general nutrition, upon the activity of the liver, and especially upon the urinary secretion, which it increases considerably.

It was hoped for a time that it would be possible to effect rapid depuration of the organism by intravenous or subcutaneous injections of artificial serum. While more profound study has demonstrated the excellent effects of this form of medication in the treatment of acute infections, it has likewise established that its action is very complex and that it affects the nervous system and general nutrition rather than the emunctories.

It is thus seen that most of the procedures above indicated are far less simple than would at first appear. They act mostly upon the organism and stimulate the general reactions. The injections of antitoxic serum or salt-water give rise to cellular proliferations which must favor the defense of the organism. Therefore, not only humoral modifications are produced, but the figurate elements are likewise acted upon. Besides the general reactions of the organism, the local

reactions which appear at the point invaded by pathogenic agents must be considered.

According to circumstances, local inflammation must be stimulated, checked, or diverted. Even acute manifestations may be stimulated. Thus, one of the best treatments of erysipelas or phlegmons consists in very hot applications. The reaction of the organism is thus increased and, consequently, rendered more rapidly efficacious. The phlogistic method is far oftener resorted to in the case of torpid lesions. Certain suppurating foci, certain tubercular lesions, or ulcerations of any description, are treated by hot applications, scarifications, and cauterizations. These procedures bring about recovery by awakening an inflammation which had prematurely ended. In other instances this effect is secured by means of toxic substances. Potassium cantharidate and tuberculin stimulate atonic tubercular lesions. Or we may act by producing a microbic inflammation. We have sufficiently studied this question in connection with microbic associations and shown notably the curative rôle of erysipelas.

In cases in which local reaction is too intense, it is evidently necessary to moderate inflammation. This is particularly indicated when the lesion occupies an important organ and threatens life by disturbing its function. It is usual to apply refrigerants and especially ice continuously over the cardiac region, the abdomen, and the head in cases of pericarditis, peritonitis, or meningitis, respectively. Peri-inflammatory or pre-inflammatory congestion is also combated by blood-letting, antiphlogistics, and vasomotor medicines. While nitrites are utilized to stimulate reactions, vasoconstrictors, such as ergotin, are employed to restrain them. Finally, a derivation may also be brought about. When an inflammation is too intense, a revulsion at a more or less distant point can be induced. This may sometimes be in the area of the skin corresponding to the diseased region, where thermocauterization or mustard plaster is to be applied. On other occasions the digestive canal may be acted upon, for example, by means of purgatives. Thus a sort of metastasis is artificially produced.

We cannot, therefore, in an exclusive manner assert that reactions must be combated or stimulated. It is only necessary to remember that inflammatory actions are always useful. They represent a means of defense. It is to be noted, however, that their intensity may exceed the object. We may then conclude that reaction must sometimes be combated, often stimulated, and always directed.

Although the medications, the general laws of which we have just indicated, are the most rational, symptomatic therapeutics must not be despised. The latter consists simply in remedying immediate accidents, in combating certain disturbances without reascending to their cause or point of departure. Although it must frequently be considered as an acknowledgment of our ignorance, this method is at times the only possible and even the only admissible one. When we are confronted by accidents which threaten life we must resort to urgent medication directed against the disorder observed without looking for its origin. When the physician is called to the bedside of a patient who is suffocating, and he has recognized by the characters of respiratory embarrassment that it is dependent upon laryngeal stenosis, his first thought should be to re-establish the course of the air and immediately perform tracheotomy. He may subsequently investigate the cause of the stenosis.

Symptomatic therapeutics may serve as an auxiliary, and is then perfectly justifiable. A patient suffering from syphilitic cephalalgia must receive specific treatment. As, however, the latter requires several days to produce its effects, symptomatic medication is at the same time to be resorted to in order to relieve the nocturnal exacerbations of pain and procure rest to the sufferer. To this end, along with 60 to 90 grains (1 to 6 grams) of potassium iodide directed to the syphilitic element, some hypnotic should be prescribed to relieve the headache.

It is perfectly rational symptomatic medication to prescribe opium for cough, atropine for sweating, enemas or purgatives for constipation, and analgesics for pain. In all these cases symptomatic medication assists therapeutics. It is, therefore, perfectly justifiable. On the other hand, however, it is an avowal of our impotence if we are contented with treating a symptom because we are unable to recognize its mechanism or trace it to its cause.

Among the symptoms which most frequently call for treatment, fever deserves special mention. The rise of temperature is painful for the patient, it causes anxiety to the family, and preoccupies the mind of the physician. Apprehension is felt that hyperthermia will give rise to serious accidents if too intense and allowed to persist. Moreover, since the use of the thermometer has become a daily practise, it is one of the disturbances which is most readily detected. There is, therefore, an inclination to direct all efforts against it. This inclination is expressed by the introduction into therapeutics of a

prodigious number of febrifuges. But it seems to be demonstrated to-day that the cellular lesions which were once attributed to fever depend rather upon the toxic cause which engenders fever, and that hyperthermia is, in reality, not so dangerous. At any rate, most of the febrifuges, excepting specific ones, act upon the mechanism and not upon the cause. As a rule, they hinder salutary reactions, diminish oxidations, and consequently exert an unfavorable influence. Exception is to be made only of cold bathing, which alone is rational, since it lowers the temperature by abstracting heat. In connection with pathological physiology, we have shown that, in fever, the dissipation of heat is increased. Cold bathing further increases and thereby completes the work of defense undertaken by the organism; it thus enters into the domain of natural medication.

General Rules of Therapeutics in Infections. The therapeutics of infectious diseases is based upon clinical observation and experimental research. Formerly attempts were first made upon diseased men. The old physicians, led by theoretical ideas which were often erroneous, or assisted by some happy coincidence, tried a great number of medicinal substances. Some of these, having proved really efficacious, are still employed. At times we utilize them without knowing exactly by what mechanism they act. Tradition having established their rôle, we cannot blame empiricism directing this course of action. Sometimes experimentation immediately demonstrated the mode of action of the medicine or explained and justified its employment. Formerly experimentation upon animals followed the application to man. At the present day therapeutics must adopt a reverse course and always begin with experimental study. The latter informs us as to the toxic and pharmacodynamic action of the medicine. It therefore has a double object.

In order to determine the toxic equivalent of a substance, it is necessary to experiment upon animals of different species. We cannot be too cautious when acting upon man. The fatal dose is determined by intravenous injection, and for certain medicines the dose which is immediately fatal and that which is ultimately so should be ascertained. It is necessary to know that certain substances, even when injected into the veins, produce no, or only slight, disturbances. If, however, the dose is increased, the animal dies a few seconds after injection or even while the toxic substance is still being introduced. With certain substances, if the intravenous injection is arrested at the moment when the fatal dose is approached, the

symptoms disappear and the animal recovers. However, such is not always the case. There is often a period of latency during which the animal appears to be in good health. After a variable length of time disorders are produced and terminate in death. The poison did not act immediately, and perhaps it underwent previous transformation within the organism. Be that as it may, the dose which is tardily fatal is often considerably smaller than the one immediately fatal, and, for the physician, this is a point of great consequence.

As intravenous injection of medicines is seldom employed, it is indispensable, after studying the toxicity of the substances injected into the blood, to investigate their action when they are introduced by other channels, notably beneath the skin or into the alimentary canal. The rôle of absorption, the influence of transformations which may occur within the gastrointestinal cavity, in contact with aliments, secretions, and microbes which multiply there, may modify the composition and consequently the action of medicines. When absorption has taken place, the substance, before reaching the points upon which it acts, passes through certain glands which may further modify its composition or its action. Among the latter are the liver and lungs.

These are sufficient reasons for multiplying the experiments and injecting the poison by the most varied channels. It does not suffice, however, simply to notice the effects of a single dose. In general, the physician prescribes a medicine for several days in succession. The experimenter must, therefore, administer the substance for a certain length of time, and, if no disturbance results, he must not yet declare the substance to be harmless. He must observe the animals and kill some of them in order to learn whether there are produced in their organs lesions unexpressed by any symptom and which can be determined only by histological examination.

These preparatory studies are very tedious and delicate. It seems to us, however, that they are indispensable when it is desired to make therapeutic application to human beings. It is to be noted, however, that these first investigations teach us only the dangerous and harmless doses. After determining these first points, namely, after solving the toxicological problem, the pharmacodynamic study is to be undertaken. Assisted by all the modern scientific data, an inquiry into the modifications of the medicine within the organism, its channels of elimination, its action upon the fluids, tissues, and organs may be made. In this connection, chemical analysis on the

one hand, and on the other physiological analysis and, notably, the graphic method, must intervene.

The rules just referred to are general rules applicable to all therapeutic studies. When the treatment of infections is reached these rules require to be completed with some particular data.

Since we can produce in animals a great number of infectious diseases we must no longer pursue our studies by operating upon healthy but upon infected animals.

The necessity of investigations of this sort appears when it is believed that a medicine capable of curing a disease has been found. It is then necessary to inoculate a certain number of animals, some of which are to be kept as controls and others to receive the medicinal substances. The results thus obtained are of great value, since experimental infection is always simpler than a spontaneous infection. It is monomicrobic, while in man the disease often results from an association of microbes. The treatment may be begun as soon as is desired, while in spontaneous infection the first symptoms are often belated and appear a long time after contamination. Lastly, the use of control animals gives undeniable value to experimental results, while in clinical experience we may clearly see what is produced as a result of the treatment, but we do not know what would happen in case of abstention.

Nevertheless, we must not conclude that the successes are the same in both cases, for the reason that clinical cases are complex, and treatment is often commenced too late, or the organism is affected by taints or previous lesions. Clinical observation must pronounce final judgment, and, too often, it establishes an apparent antagonism between practical application and experimental results.

When it is desired to determine the action of antimicrobic or antitoxic substances the pharmacodynamic action is often discarded and an attempt is made to solve the following three problems: What is the action of the substance upon the microbe or the toxin outside the organism? What is its toxic action upon the healthy animal? What is its curative action upon the diseased animal—*i. e.*, upon the infected or intoxicated animal?

The rules which govern the solution of the last two questions are the general rules which we have already exposed. As to the first problem, if the question concerns an antiseptic substance, it is customary to investigate the effect of artificial media upon the vegeta-

tive property of the microbe. Inoculations into animals should be next undertaken, for microbes which are so altered as to no longer develop in a culture bouillon may sometimes be still sufficiently active to vegetate within the organism. On the other hand, microbes which are incapable of overcoming the resistance of the economy may still be able to live in inert media. The great principle of attenuation of viruses is based upon this fact.

When antitoxic substances are under study, experimentation is the only method which reveals the modifications produced. The toxin and the antitoxin are injected into the animals simultaneously and successively. These principles are daily utilized in the study of therapeutic serums.

It is certain that the method furnishes excellent indications. Although, in this case, experimentation approaches clinical observation as nearly as possible, the facts do not and cannot altogether correspond. The experimental results obtained with serums are always more brilliant than those observed clinically. The reason is that clinical facts are always complex. Hence, even when a great number of specific serums have been prepared, it will still be necessary to resort to medicines intended to palliate certain disturbances and to combat certain accidents.

Unfortunately, the substances which are used in this case have been studied only upon healthy animals. It would, therefore, be interesting to repeat their study upon infected animals from the double standpoint of toxicology and pharmacodynamics. It is necessary, in fact, to determine whether the medicine has the same toxic property in the diseased and the healthy animal, and whether this toxicity is modified by the different periods of the disease. It is also necessary to inquire whether the medicine always acts in the same manner, whether infection does not modify its mode of action. Here, we believe, is a large field open to experimenters. As few researches have been made upon this point, we have believed it would be of interest to study what becomes of the resistance of animals through strychnine in the course of anthrax infection, and then to undertake analogous researches with strychnine and chloral in animals suffering from tetanus. From our experiments we may draw the conclusion that chloral may be employed to palliate the painful phenomena produced by tetanus, but it is not a truly curative medicine.

Antiseptic Method.

The object of the antiseptic method is to destroy the pathogenic agents by acting directly upon them and indirectly by modifying the organism. When it is incapable of destroying these agents, it opposes their multiplication or hinders their harmful action. We know at present that microbes act only by their soluble products. The history of antitoxic substances which neutralize or diminish the action of toxins may, therefore, be considered as supplementary to the study of antiseptics.

Antisepsis by Physical Agents. The indications of antisepsis may be realized by procedures of a physical order. As is known, heat is the surest agent for destroying microbes. Unfortunately, although it is daily employed for sterilizing inert substances, it is too difficult to manage when applied to the living organism. While very hot local applications hinder infections; they accomplish this simply by modifying circulation. They act upon the microbes in an indirect manner. When, however, the lesion is well circumscribed, it is possible to destroy it by thermocauterization. Folliculites are thus cured. If the lesion is extensive, a red-hot iron can be used, as is done for certain phlegmons and gangrene. It is, perhaps, possible to combat infections of serous membranes by very hot-water irrigations. It is possible to inject into the peritoneum or the veins of animals salt water at a temperature of 122° F. (50° C.) or 131° F. (55° C.) without any inconvenience. We should not, however, rely too much upon these different methods, since heat coagulates albumins, and the minute particles thus formed protect the pathogenic agents. Moreover, when it is intense, heat cannot be applied, except to circumscribed points, and, consequently, it acts upon a very restricted area of the diseased tissue.

There are certain viruses which are much more sensitive to heat than the neighboring tissues. Thus the investigations of Dr. Aubert show that 100.4° F. (38° C.) is sufficient to check the multiplication of the bacillus of soft chancre. At a temperature of 104° F. (40° C.) the microbe is killed. Hence, by employing this temperature, which is not harmful for the tissues, we may rapidly cure a soft chancre. A variant of this method consists in treating the lesion by means of overheated air.

Microbes withstand cold far better than heat. Hence, cold applications, although they sometimes modify the vitality and the inflam-

matory reactions of the tissues, exert no influence whatever upon the pathogenic elements. When the germicidal action of the sun's rays were revealed, the influence of light upon the course of infections was investigated. The problem is complex, however, since the action exerted upon the organism and upon the microbes is to be taken into account. Interesting attempts have nevertheless been made with the object of utilizing certain properties of sunlight. Finsen has become the champion of the phototherapic method. An attempt has also been made to cause patients suffering from variola to sojourn in wards provided with red glass windows. The results have not been very encouraging. On the other hand, quite remarkable results have been obtained by treating lupus patients with colored sun-rays.

Antisepsis by Chemical Agents. Chemical antiseptics are extremely numerous, and certain among them were known and employed in olden times.[1] In the days of Hippocrates wine and aromatic oils and certain caustic iron and copper salts were employed for washing wounds. The same substances were much used in the middle ages. Later, cinchona powder, mercurial, arsenical, and astringent preparations, as well as balsams and resins, came into use.

We must come to the time of Lister to find a true doctrine of antisepsis, at least of surgical antisepsis. Lister, taking as a basis the works of Pasteur on fermentations, assumed that the air exercised a noxious influence upon wounds by virtue of the germs which it contained and deposited in the wounds. Therefore, making use of carbolic acid, which was already employed by Lemaire, he washed his hands with a $2\frac{1}{2}$ per cent. solution, immersed his instruments in a stronger solution (5 per cent.), washed the field of operation with a strong solution, and during the operation directed upon the field a spray of carbolic acid. He then introduced drainage tubes sterilized by means of carbolic acid. Lastly, after covering the wound with a protective bandage, he applied carbolized gauze and impermeable mackintosh tissue.

At present the principles laid down by Lister are modified and his procedures are abandoned. The germs of the air are not feared as they were formerly. The pathogenic agents present upon the skin of the patient are more to be feared, and especially those found upon the hands of the surgeon and his assistants. Therefore, the spray

[1] Weiss. Contribution a l'étude des méthodes servant a déterminer le pouvoir antiseptique. Thèse de Paris, 1900.

was first done away with; next, the instruments and the dressings were successfully sterilized by heat; then the use of antiseptics was gradually abandoned, and in a word, asepsis was substituted for antisepsis. This is at least what is done in surgical operations when diseased but not infected parts are operated upon. When, on the contrary, parts invaded by pathogenic germs are dealt with, antisepsis is still utilized. It has been recognized, however, that strong antiseptics are to be avoided, because of their caustic action, which is more harmful to the tissues than to the microbes. In most cases it is sufficient to resort to profuse lavage with boiled water, which acts mechanically by carrying away the germs and their toxins as well as the degenerated cells contained in the morbid focus.

While antisepsis has lost its first importance in surgery, it is still held in great esteem in medicine. Attempts have been made to kill, at least partially, the germs swarming in the digestive canal and those which may invade the respiratory or urinary apparatus. Even general antisepsis of the organism has been aimed at by some practitioners. It is, therefore, important to have at one's disposal a certain number of antiseptic substances.

An antiseptic must fulfil certain general conditions and, according to the use for which it is destined, possess particular properties. The general properties of all antiseptics are the following: to be harmful for the morbid germs; to be harmless for the animal cells with which it comes in contact; not to form with the organic elements combinations which render them inoffensive for microbes; not to coagulate albumins the particles of which protect the bacteria.

The particular properties may be diametrically opposed according to the case. According as we have to sterilize a closed cavity or a surface, to act upon a limited area, or, on the contrary, to extend the germicidal action to distant parts, to treat the alimentary canal, the urinary or respiratory apparatus, we must employ soluble or insoluble, diffusible or non-diffusible, liquid or solid, pulverulent or volatile substances.

The problem which might at first view appear quite simple is, therefore, very complex. We must study antisepsis itself—*i. e.*, we must determine the action of each substance upon microbes; then establish its toxic equivalents and investigate the therapeutic indications to which it may respond.

The determination of the antiseptic power of a substance is not as easy as may be believed. The results vary according to the

microbe which is operated upon and the conditions under which we are placed. It is evident that the same amount of an antiseptic will have different effects according as it acts upon more or less sensitive species or upon cultures provided with or deprived of spores. Finally, for the same culture, we must take into account the number of microbes upon which the effects of the antiseptic substance are exerted.

In order to study the action of an antiseptic, many experimenters add a certain quantity of it to a culture medium, and then cultivate in the latter a particular bacterium. It is too often forgotten, however, that, under these conditions, the solid or liquid medium employed has not a fixed constitution, and that the results may vary from one day to another. It is, therefore, better to make use of solutions of constant composition, for instance, a mineral solution to which a pure peptone is added. The medium being definite, the addition of the antiseptic substance may produce a precipitate which annihilates the action of the germicidal substance, or the latter may enter into a more or less stable combination calculated to diminish its power or to reduce the nutritive property of the medium. It is also to be remembered that the surrounding temperature exerts an important influence upon the development of the microbe. At a certain degree it favors its vegetation; as it advances, however, it increases the germicidal action of the antiseptic. Thus, to cite only one example, Chauveau and Arloing have shown that a 3 per cent. solution of carbolic acid exerts no action upon the bacillus of gaseous gangrene when its action lasts for twenty-four hours at a temperature of 59° F. (15° C.). At 96.8° F. (36° C.) it sterilizes the medium within six or eight hours.

The results also vary acording as the germs operated upon are dry or moist. In the former case resistance is much greater. Dr. Chamberland thinks that the difference of action is due to the time necessary to moisten the dried microbes. In order to avoid these various causes of error another method is frequently resorted to. Platinum threads, silk threads, pieces of glass, paper, or linen are dipped into the culture to be studied. These are then exposed to antiseptic vapors or immersed in the antiseptic fluid. After a variable time the objects thus impregnated with cultures are washed with sterilized water and placed in a nutrient medium.

This method, which at first appears as simple as it is exact, in reality is exposed to grave errors. In the first place, when a culture

is spread upon any object whatsoever, the distribution is not uniform. There are thicker parts which do not undergo the action of the antiseptic, except in their superficial zone. Moreover, in spite of prolonged washing, we can never be sure of having removed all the antiseptic. A quantity sufficient to prevent multiplication may remain. Finally, Drs. Chamberland and Fernbach have shown that the results vary according to the objects used in the experiments. Germs spread upon paper die more quickly than those distributed upon glass, while those that are found upon linen resist for a still longer period of time. E. Weiss advises addition of the antiseptic to a bouillon culture, then to take from the latter a small drop and put it in a large amount of fresh bouillon. The trace of antiseptic thus introduced is insignificant. This method is in fact sufficiently exact and has the advantage of great simplicity.

When the substance to be studied is insoluble in culture media we are obliged to dissolve it previously in some liquid like alcohol or ether. The results then will vary according to the nature of the solvent. Finally, when it is volatile, we must take a series of precautions in order to prevent evaporation during the experiment.

These few considerations show how complicated the problem which is apparently so simple becomes when we desire to study it with some accuracy. We must also remember that microbes become habituated to the substances that are harmful to them, so that by making cultures in series in media charged with antiseptics the multiplication of the germs becomes progressively easier.

An antiseptic substance produces quite different effects according to the amounts employed. These effects may be classified in the following order: In large doses, sterilization, viz., death of the microbes, occurs. Next, when the doses gradually diminish, infertility of the medium occurs—*i. e.*, the microbe remains living, but it cannot multiply; when, however, it is transferred to another medium, it again multiplies. In another class of cases the microbe develops, but the colonies appear tardily and are small in number. At the same time the functions are disturbed. The pathogenic agents become attenuated, and we have already shown that the addition of antiseptics represents a method for the transformation of viruses into vaccines. At all events, it is very easy to appreciate the functional modifications produced by antiseptics in studying the chromogenic bacteria. Amounts which permit multiplication prevent the appearance of pigment.

Finally, there is a result analogous to facts observed when studying the action of poisons upon animals. Antiseptics in very minute amounts, far from hindering the function of microbes, stimulate it to a notable degree. We have shown, for example, that a trace of corrosive sublimate favors the production of red pigment by the B. prodigiosus.

The experiments performed with a view to determine the value of antiseptics are innumerable. In order to fix the ideas, it will suffice to borrow some figures from Mequel's scale of antiseptic power. This author has investigated the amount of antiseptic capable of opposing the putrefaction of one quart (litre) of bouillon. We shall mention only the substances most frequently used in medicine:

Eminently antiseptic substances	Mercury biniodide	0.025
	Silver iodide	0.03
	Peroxide of hydrogen	0.05
	Bichloride of mercury	0.07
	Silver nitrate	0.08
Very highly antiseptic substances	Osmic and chromic acids	0.15
	Chlorine, iodine, cyanhydric acid	0.25
	Bromine, iodoform	0.60
	Bromoform	0.7
	Chloroform	0.8
	Copper sulphate	0.9
Highly antiseptic substances	Salicylic and benzoic acids	1.0
	Picric acid	1.3
	Zinc chloride	1.9
	Thymic acid	2.0
	Sulphuric, nitric, and hydrochloric acids	2 to 3
	Carbolic acid	3.2
	Potassium permanganate	3.5
	Alum	4.5
	Tannin	4.8
Moderately antiseptic substances	Arsenious acid	6.0
	Boric acid	7.5
	Chloral hydrate,	9.3
	Sodium salicylate	10.0
Slightly antiseptic substances	Sulphuric ether	22.0
	Ethylic alcohol	95.0
	Potassium iodide	140.0
	Glycerin	225.0
	Sodium chlorate	400.0

It is well to add to this list oils the properties of which were already known to the ancient world, and were employed especially for purposes of embalming. We are indebted to Dr. Chamberland for very interesting researches on their antiseptic action. According to this scientist, six of them are the leading oils, viz., the essence of origanum, China cinnamon, Ceylon cinnamon, Angelica, vespetro, and geranium.

Behring has studied the relationship between the toxic and antiseptic power of bacillus anthracis, and has concluded that the relative toxicity hardly varies. It oscillates around the figure 6. That is to

say, in order to kill one kilogram of animal the substance required is six times smaller than is required for sterilizing one quart (1000 cubic centigrams) of liquid. Here are a few figures given by him and which may present a certain interest from a practical standpoint:

	Antiseptic Power.	*Toxic Power.*	*Relative Toxicity.*
Carbolic acid	1.7 gr.	0.27 gr.	6.6
Corrosive sublimate	0.1 gr.	0.017 gr.	5.8
Chlorohydrate of quinine . . .	0.8 gr.	0.17 gr.	4.7
Mercurocyanide of potassium . .	0.017 gr.	0.003 gr.	5.6
Argentocyanide of potassium . .	0.02 gr.	0.003 gr.	6.6
Aurocyanide of potassium . . .	0.04 gr.	0.006 gr.	6.6

In determining the toxic properties possessed by antiseptics we must not be contented with the results obtained in animals. It is likewise necessary to remember that man presents a peculiar sensitiveness which varies from one subject to another. All antiseptics may produce erythemata, a few may cause urinary disorders, as is the case with carbolic acid, and lesions in the mucous membranes of the mouth and large intestine, such as is the case with corrosive sublimate. Without dwelling upon all these accidents, which are well known and have often been described,[1] we shall cite an observation which shows the susceptibility of certain subjects to antiseptics. In consequence of a slight traumatism a young man was treated with applications of a mild solution of corrosive sublimate. At the end of forty-eight hours the arm was so red and swollen that it was thought to be a case of erysipelas, and the sufferer was therefore sent to our wards. We there corrected the diagnosis, and, remembering that the skin already irritated by the application of some antiseptic cannot well tolerate the use of other substances, we prescribed simply application of boiled water. The symptoms improved quite rapidly. We then vaccinated the patient, and before the inoculation, we washed the arm with Van Swieten's solution. On the following day we found the part of the skin which had come in contact with the mercurial solution red and swollen, and, what was altogether characteristic, the drops of the solution had flowed along the arm and had marked their passage in the form of lines of small pyriform plates of an intense red color. Thus, when an antiseptic is to be employed the choice must be governed in view of the region to which it is to be applied and according to the effect which is aimed at, the microbe which is to be acted upon, and the special sensi-

[1] To see notably the "Thèse d'aggrégation" of F. Brun. Des accidents imputables à l'emploi chirurgical des antiseptiques. Paris, 1886.

tiveness of the individual, if this is known by his previous experience. It is also to be remembered that it is often advantageous to combine several antiseptics in one solution, for their power against the microbes increases more rapidly than is indicated by the sum total of the components, while just the contrary is true as regards the toxicity. It is well to recall that hot solutions are more effective and that it is often advantageous to add to the liquid substances which prevent coagulation of the albumins. Lastly, at the end of a certain period of time, the antiseptic action seems to be exhausted, and some other substance must then be employed.

These general rules will find their application in the rapid review which we shall give of the antisepsis of various parts of the body. In this exposition we borrow a great number of documents from Prof. Bouchard's lectures.[1]

Antisepsis of the Skin. Antisepsis of the skin has long been appreciated, and the ancient lawgivers laid stress upon the usefulness of ablutions. At the present time the practitioner often utilizes antiseptic bathing. He sometimes employs naphthol water in the dose of 10 drams for a bath of 200 quarts (40 grams in 200 litres) or a bath with corrosive sublimate water. The use of this last substance has the inconvenience of requiring special bath-tubs. The proportion is 2.50 to 5 drams (10 to 20 grams) of corrosive sublimate mixed with the same amount of chlorhydrate of ammonia, which makes a proportion of 0.05 to 0.1 per thousand. Baths with corrosive sublimate are daily employed in our hospitals for disinfecting the skin of convalescents. They may also be used in the course of certain infections characterized by cutaneous manifestations. They are most frequently used in the treatment of variola. In this infection, however, we give preference to naphthol baths. Naphthol dissolved in alcohol should be poured into the bath-tub. A bath lasting a quarter of an hour is given at the beginning of the disease. Secondary infections are prevented in this way. Antiseptic bathing is at present recognized to be the best treatment of pustular variola.

Naphthol baths also render important service in cases of extensive superficial lesions. The author employs them against the wandering type of erysipelas as well as in furunculosis, which is so frequent in consequence of certain infections, such as variola and varicella.

[1] Bouchard. Thérapeutique des maladies infectieuses. Antisepsie, Paris, 1889.

It is hardly necessary to state that local baths may be prescribed in cutaneous lesions upon the extremities. This manner of bathing gives gratifying results in the treatment of panaris, lymphangites, erysipelas, and phlegmons on the limbs. According to requirements, the baths are given with corrosive sublimate, carbolic acid, or potassium permanganate. In the intervals of the baths compresses dipped in a slightly antiseptic liquid are applied to the affected parts. In lesions with gangrenous or putrid tendency the author uses with advantage compresses moistened with peroxide of hydrogen. Equal parts of commercial peroxide of hydrogen and four per thousand sodium bicarbonate solution are mixed; thus the fluid is neutralized, and is then brought to six volumes by addition of four parts of water.

It should be remembered that antiseptics are not always well borne by the skin, that they often give rise to intense and rebellious dermatites, and that the local medicinal lesion is often the starting point of an extensive and generalized erythema. In such cases an application of another antiseptic only intensifies the inflammation, and, by diminishing the resistance of the skin, favors the development of secondary infections. Under such conditions use should be made simply of sterilized compresses dipped in boiling water, poultices, and in certain cases, salves prepared with perfectly neutral vaseline.

Antiseptics applied to the skin act only upon the surface. In certain cases they arrest infection of cutaneous glands. Thus, for instance, applications of tincture of iodine often abort the development of furuncles. Do they, however, act as antiseptics or as stimulants? Better results are obtained simply with alcohol. In persons who are subject to furuncles or acneic pustules in the neck, energetic friction with some alcoholic tincture every morning is prescribed. The results are generally very good. Alcohol renders valuable service in the treatment of all small lesions of this kind. Thus absolute alcohol saturated with boric acid is successfully employed against folliculites, sycosis, furuncles of the auditory canal, etc.

In order to act upon the deeper parts of the epidermis, mechanical procedures, such as friction and brushing, may also be resorted to. This is currently practised in surgery for disinfecting the field of operation. When infection occurs this procedure is no longer of any use. It has, therefore, been thought that the antiseptic would better penetrate if thrown in the form of jets. Thus carbolized spray is employed in anthrax, and corrosive sublimate spray in erysipelas.

Antisepsis of the Genital and Urinary Organs. Antisepsis of the genital organs occupied the attention of ancient lawgivers as much as that of the skin. In the law of Moses, purification after each physiological or pathological flow or discharge was prescribed. Confinement, menstruation, and nocturnal pollutions rendered the individuals impure. The law prescribed for the priest bathing after sexual intercourse. It is evidently as an antiseptic measure that certain religions have ordered circumcision.

At the present day it is customary to wash the external genital organs and to irrigate the vagina for purposes of cleanliness. The rules which must govern the disinfection of the genital organs are almost the same as for the skin. For the treatment of balanitis in man, injections are made between the foreskin and the glans penis, but fluids containing alcohol should be avoided, since their contact with the genital mucous membrane is very painful. Weak solutions of potassium permanganate, corrosive sublimate, silver nitrate, protargol, or a 20 per 1000 solution of liquid subacetate of lead are used in most cases. In women, under pathological conditions, the vagina is disinfected by injection of the same substances or by application to the mucous membrane of gauze or cotton tampons. If the infection involves the uterus, antiseptics are more frequently employed. According to the requirements of the case, the cervix of the uterus may previously be dilated by means of a canula, and lavage given with weak antiseptic solutions. In certain instances continuous irrigation is resorted to according to the method of Drs. Pinard and Varnier. The substances most frequently employed are the bichloride or biniodide of mercury, carbolic acid, and permanganate of potassium in the proportion of 1 : 10,000. Mercurial salts often produce disturbances which are easily overlooked because they are wrongly attributed to the infection which is being combated. Thus, dysenteriform symptoms have sometimes been induced by mercurial ulceration of the large intestine.

Antisepsis of the uterus and bladder may be practised according to two different procedures: Medicinal substances may be injected or ingested; in the latter case the medicine reaches the bladder when eliminated through the urine. Antisepsis of the urethra is hardly ever practised except in cases of gonorrhea. At the beginning of the infection, the abortive method may be resorted to. This generally consists in injecting a 1 or 2 per cent. solution of nitrate of silver. In one-third of the cases this method proves successful. At a later stage

injections are used, the formulæ of which are innumerable. Recently, however, they have been replaced by profuse irrigations with 1 4000 solution of potassium permanganate. These irrigations may be prescribed from the very beginning of the disease, except when the infection is particularly acute. In this instance the lips of the meatus are swollen and the canal is hard. Then the first treatment must be emollient. Later on, when the acute phenomena have subsided, the chronic lesions quite often persist. Gonococci then multiply in the prostate gland. Under such circumstances massage of the organ is practised; fifteen to twenty drops of a 2 per cent. solution of silver nitrate or forty to sixty drops of a protargol solution of the same strength are introduced. Finally, antisepsis of the urethra may likewise be effected by medicated bougies.

Irrigations analogous to those employed for the urethra find application in the treatment of vesical affections. Permanganate, protargol, or simply boric acid are mostly used. These irrigations act mechanically rather than chemically. A healthy bladder is only exceptionally infected. In the great majority of cases cystitis results from unclean catheterization in individuals in whom the bladder empties itself poorly—*i.e.*, in those who suffer from stricture of the urethra and particularly from prostatic hypertrophy. Stagnation of the urine favors multiplication of the germs. Irrigations, therefore, no matter what kind, have the great advantage of suppressing the principal cause which induced and sustained the infection.

Antisepsis of the urinary passages, ureter, bladder, and urethra may be effected by the administration of substances which may be eliminated by the kidneys. Balsams, such as copaiba, cubebs, santal, and turpentine, are daily employed for this purpose. Lastly, salol, which is broken up in the intestine into carbolic and salicylic acids, is also used. Elimination of the substances through the urine realizes a slight antisepsis and renders valuable service in the treatment of cystites.

Antisepsis of the Mouth. Antiseptic Treatment of Stomatites and Anginas. The organs and cavities of the face are easily invaded by pathogenic germs. Hence the usefulness, even under normal conditions, of practising antisepsis of these parts in a certain measure. Greater care is naturally given to the buccal cavity.

Even in health it is indispensable to cleanse the mouth and the teeth frequently. It is well, for instance, to cleanse the teeth in the

morning, in the evening, and after each meal. Brushes are generally employed for this purpose, which have the great inconvenience of retaining organic particles liable to a rapid putrefaction. This is remedied by washing the brush with some antiseptic solution. A good one is thymic acid in the strength of 1:3000. In the course of infectious diseases the care of the mouth requires special attention. The dryness of the mucous membrane diminishes its means of protection and favors the multiplication of germs which tend to invade the deeper parts and penetrate through the excretory ducts, notably the parotid gland. It will, therefore, be well to prescribe frequent lavage with an alkaline water, viz., with bicarbonate or borate solutions. Antisepsis is not realized thereby, but the mucous membrane is thus indirectly placed under better conditions of resistance. Fermentation of carbohydrates found in the mouth produce acids which harm the epithelium. By neutralizing these acids the alkalies act in aphtha. While it is true that the fungus producing this stomatitis lives preferably in alkaline media, the observation by Gubler that it develops in the mouth when the medium becomes acid and ceases to multiply when the latter is rendered alkaline, is simply due to the fact that acids diminish the vitality of the mucous membrane, and not, as has long been asserted, because they favor the vegetation of the fungus.

When infection is more profound, profuse lavage of the mouth is generally practised. The patient sits up, inclines the head forward while the antiseptic fluid is thrown into the mouth. A good many mixtures have been proposed. In our wards we employ in stomatites and anginas a solution containing 10 per 1000 of carbolic acid and 1 per 1000 of thymol. Solutions of chloral hydrate, 1:100, are also very good. When microbic lesions are already developed applications of antiseptic or caustic substances should be made. In stomatites, whatever their nature may be, cauterizations by alum, nitrate of silver, and especially salicylic acid, are practised, the latter being used in the proportion of 1:10 dissolved in a mixture of equal parts of alcohol and glycerin. Phenol, or sulphoricinated[1] salol, or tincture of iodine are also useful. We have often obtained satisfactory results from the employment of tincture of cochlearia.

There is a special form of gingivitis—expulsive gingivitis—which

[1] There is a French preparation, "acide sulforicinique," composed of oleum ricini and sulphuric acid. Antiseptic substances, such as salol and phenol, may be combined with this acid to form sulphoricinated salol, or phenol, etc.—Translator.

is very grave because it causes shedding of the healthy teeth. It should be treated by strong antiseptics, such as carbolic, salicylic, or chromic acid. Finally, such antiseptics as creosote, methyl salicylate, and arsenious acid are employed for the treatment of dental caries.

In most cases of anginas antiseptic lavage is sufficient. In persistent lesions, however, painting with more energetic antiseptics is indicated. Tincture of iodine, salol, hydroglycerinated solutions of corrosive sublimate, and camphorated naphthol are the substances most frequently employed. It is well, however, not to prolong their use, since they produce irritation and maintain the lesion against which they are directed. The therapeutic indications are the same in suppurating tonsillites. Gargles or, still better, slightly antiseptic lavage, is also prescribed. In some cases puncture of the abscess is at a certain moment to be practised. An emetic is sometimes administered for this purpose, but this medication acts only when the lesion is at the point of opening spontaneously. It is then useless and, what constitutes a graver objection, it has the inconvenience of depressing the patient.

Unlike the buccal cavity, the nasal cavity does not need antiseptic lavage in health. In the course of infectious diseases it is well to introduce a slightly volatile antiseptic substance. Mentholated olive oil in the proportion of 1:40 fulfils this indication; every morning five or six drops of it are introduced into the nostrils. A salve containing twenty grams of vaseline, one gram of resorcin, and half a gram of menthol is also employed. When the nasal fossæ are more particularly affected, whether the lesion be primary or secondary, antisepsis is likewise indicated.

Simple coryza is often cured when slightly antiseptic powders are employed from the beginning. Many formulas have been given. The author generally employs a mixture made with equal parts of pulverized boric acid, benzoin powder, and salicylate of bismuth. Ten grams of each of these substances are prescribed, and a half gram of hydrochlorate of cocaine is added.

Serious rhinites are sometimes observed in the course of certain infections. The purulent rhinitis of scarlatina represents a very important cause of death. Its treatment must be energetic. We have recourse to lavage with peroxide of hydrogen. In order, however, to insure cleansing of the nasal fossæ, flow of the discharge from within outward must be secured. Inflammation of the nasal fossæ

may spread it to the sinuses of the face. This complication may readily be recognized by the following two symptoms: a purulent discharge from one nostril and a facial neuralgia. The treatment consists in causing the patient to inhale through the diseased nostril by means of a funnel turned upside down upon a bowl of hot water into which has been poured a teaspoonful of a 4 per cent. alcoholic solution of menthol. The inhalations are repeated hourly; each sitting should last five minutes. If the inflammation involves the Eustachian tube and the middle ear this new complication should be combated by paracentesis of the tympanum and irrigation. In our wards we employ lavage with borated water, which is followed by the introduction of a few drops of carbolized glycerin. We have recently obtained highly satisfactory results from lavage with a 1:500 solution of methylene blue.

Finally, in order to conclude what we have to say about antisepsis of the face, we shall recall what care is to be given to the ocular apparatus. Conjunctivites are frequent in infections; they are, however, generally benign. They heal under use of simple washings with hot borated water, followed by an occlusive dressing. In case of severe pain, a drop of a collyrium made with neutral sulphate of atropine is instilled into the eye.

Three infections frequently give rise to grave lesions of the eyes. These are zona, variola, and gonorrhea. In the case of zona, atropine and absolute occlusion of the eye are prescribed. Variola often produces purulent conjunctivites, the principal danger of which is consecutive keratitis. For conjunctivitis we employ lavage with 1:8000 solution of potassium permanganate, 5:1000 solution of protargol, or 1:500 solution of methylene blue. Should keratitis supervene, methylene blue alone is applicable. At the same time atropine is utilized to some extent.

The treatment of purulent gonorrheal conjunctivitis consists in applications of silver nitrate or protargol.

Antisepsis of the Respiratory Passages. Antisepsis of the respiratory passages may be realized: (1) by inhalations of volatile substances; (2) by directly introducing liquids or powders into the upper parts or, in the case of the lungs, by injecting them directly into their parenchyma; (3) by turning to profit elimination through the alveoli of certain volatile principles which may be introduced into the organism by any channel.

Inhalations of volatile substances are daily employed in the treat-

ment of laryngeal, tracheal, or bronchial infections. Menthol is commonly used. A 4 per cent. alcoholic solution is made use of. A dessertspoonful of this is put in a bowl of hot water and the latter covered with an inverted funnel, and inspiration made through the tubal part of the funnel. Another method consists in causing the patient to breathe an atmosphere charged with medicated vapors. Tar is often employed for this purpose. Dr. Tapret has proposed to have patients, particularly tubercular subjects, sojourn in rooms in which a 10 per 1000 creosote solution is sprayed. We may also mention sulphurous waters, which are employed in chronic infections. In other instances water charged with antiseptic substances is sprayed in front of the mouth of the sufferer. Naphtholated water (naphthol 0.25, alcohol 25 grams, water 75 grams), Van Swieten's solution, 1:1000 solution of biniodide of mercury, carbolized water, and water charged with oil of turpentine or creosote have also been utilized.

The respiratory tract being largely open to the exterior, medicines may easily be introduced therein. This is currently done as regards the larynx. Antisepsis is thus realized just as in the case of a surface exposed to the air. As regards the more deeply seated parts, we have to be contented with injecting a few drops through the larynx or, in the case of tracheotomy, through the tracheal wound. Mentholated oil in the proportion of 1 : 40 is generally employed. Should it be thought advantageous, injections by means of a needle introduced through the skin into the trachea may readily be practised.

In the presence of a well-circumscribed pulmonary focus one is always tempted to inject some antiseptic directly into it. Numerous experiments have been made in this direction, notably by Dr. Lépine and Dr. Truc. It is necessary not to exceed 1 c.cm. or 2 c.cm. beyond the surface of the lung, in order to avoid entering an important vessel. By injecting the fluid slowly it is possible to introduce a considerable amount of it. Lépine injected as much as 100 c.cm. through five different punctures. Benzoate of soda and potassium iodide have been introduced in this manner. Lépine utilized biniodide of mercury in a dose of 1:40,000. These attempts have been made particularly in pneumonia. It would be interesting, however, to renew these attempts in cases of circumscribed pulmonary gangrene.

The majority of volatile substances that are eliminated through the respiratory apparatus may exercise a medicinal action while

being eliminated, no matter through which channel they are introduced. According to this principle, it is rational to cause patients to ingest preparations of turpentine or eucalyptus, potions containing from four to six grams of hyposulphite of soda, or to administer for the same purpose sulphurous waters. According to the same idea, the use of gaseous enemata, of carbonic acid, and sulphuretted hydrogen has been advised. Too much reliance, however, should not be placed upon this method, since we have recognized, with Dr. Garnier, that sulphuretted hydrogen, even when introduced in large amounts, is not found in the exhaled air. At least it is impossible to detect the slightest trace of it by placing before the mouth of the patient a paper preparation of acetate of lead.

For the treatment of respiratory affections the subcutaneous method may likewse be utilized. Eucalyptol is often injected in this manner. Creosote is also administered either per os, or by subcutaneous injections, or through enemata. In the first case, pills of 10 centigrams are generally employed, of which three to five are taken with the two principal meals. In the second case, oily solutions in the proportion of 1 : 15 are used. Burlureaux advises to inject them slowly at the rate of forty drops per minute, which means 20 grams in an hour. As much as 100 grams and even 150 grams of the fluid have been introduced in this manner. In general it is convenient to prescribe an enema containing from $\frac{1}{2}$ gram to 1 gram of creosote incorporated in an oily emulsion. The skin may often be painted with creosote or guaiacol. Such applications are well borne when they are not too strong. They have the strange property of lowering the temperature and producing alarming manifestations if the dose of creosote is too large. The author prescribes friction with a 10 per cent. guaiacolated salve the size of a hazelnut. In fact, the recent tendency is to substitute for creosote some well-defined chemical product, such as guaiacol, or less irritating substances, such as carbonate of creosote or of guaiacol. Creosote and its derivatives render service in the treatment of all torpid infections of the respiratory passages, particularly in cases of tuberculosis. They are not without some disadvantages. Creosote sometimes produces digestive disturbances which are avoided by administering it in the form of enemas. Some authorities believe that it produces congestion and hemoptysis. Therefore, its administration is to be avoided in those cases of tuberculosis in which there is tendency to pulmonary hemorrhages. Contrary to what has been stated by some,

creosote is often useful in acute forms, and it is still the best medicine for the treatment of chronic pulmonary tuberculosis.

Antisepsis of the Alimentary Canal. The intensity of putrefactions that occur even normally in the digestive canal, the frequency and gravity of disturbances resulting therefrom, the rôle of gastrointestinal putrefactions in the development of infectious or non-infectious secondary lesions, having, apparently, nothing to do with digestive disorders, explain why therapeutists have multiplied their efforts to combat the microbes which swarm in this part of the organism. Three principal methods are now at our disposal. We may restrain fermentations by suppressing fermentable aliments. We may expel the infected remains of digestion and at the same time sweep off microbes and their toxins. Finally, we may prescribe antiseptic substances.

The digestive canal may be rendered antiseptic by means of diet. For the adult, milk diet is generally prescribed, the influence of which in this regard was clearly demonstrated by the investigations of Gilbert. In mild cases it suffices to modify the diet and restrict readily putrescible foods like meat. On the other hand, rice, vegetables, and cooked foods are prescribed. In a grave case, even milk is too fermentable. All alimentation is to be suppressed and the patient placed on water diet. This is particularly indicated in the case of the newborn suffering from gastrointestinal disturbances which at times rapidly prove fatal. Boiled water to which is added a small amount of sugar and 10:1000 of lactic acid is given. As ill-digested aliments are easily attacked by microbes, gastrointestinal antisepsis can likewise be effected, although in an indirect manner, by modifications of alimentary hygiene. It is probable that the ingestion of hydrochloric acid acts in this manner. This acid was considered as an antiseptic secreted by the mucous membrane of the stomach. The intense fermentations of hyperchlorhydria are due to the fact that the food is not well digested. Alkalies will then diminish putrefactions and, reciprocally, hydrochloric acid will play the same rôle in cases of hypochlorhydria.

Microbes may be mechanically thrown out. Profuse lavage of the stomach or intestine possesses the treble advantage of freeing the digestive canal of fermentable substances, microbes, and toxic products resulting from their multiplication. The same indication is fulfilled by the use of emetics and purgatives. The secretions and fluxes provoked by them bring about a similar cleansing. Among

purgatives calomel seems to be, in this respect, the most efficient, for it exerts at the same time an antiseptic action.

Gastrointestinal antiseptics, properly so called, may be divided from a practical standpoint into two groups: soluble and insoluble antiseptics. The soluble ones most frequently employed are sulphocarbonated water, chloroform water, and solutions of lactic and carbolic acid. It has been noted, however, that these substances as they advance in the alimentary canal are absorbed and soon disappear. Therefore, their germicidal influence is exerted upon a very limited extent of the digestive tract. Hence, it has been recommended to prescribe insoluble antiseptics, part of which may be modified and penetrate the organism, while another part passes through the whole length of the canal without any alteration.

Naphtholin was first praised. It has, however, been abandoned, for it often produces dysuria and pruritus, and may be dangerous to the sight, judging from the cataract which is caused by its ingestion in rabbits. In consequence of Prof. Bouchard's experiments, β-naphthol was utilized, instead of which, according to Dr. Maximowich, α-naphthol may be used, which has the double advantage of being more antiseptic and less toxic. The burning taste of naphthol makes it necessary to administer it in wafers. It may be given alone or associated with laxative or antidiarrheal substances. The dose is from one to three grams in twenty-four hours. It is well, however, to administer it in fractional doses, since the successive use of small doses produces a more marked antiseptic action than the same amount ingested at once, and is less irritating for the stomach. In order to avoid the inconveniences due to the caustic property of naphthol, two of the derivatives of this medicine, betol and benzonaphthol, are at present frequently made use of. Their antiseptic power is not as great, but they are well borne even by delicate stomachs, while naphthol itself has the inconvenience of causing pain and gastric burning in certain individuals. Benzonaphthol, which is the one commonly employed, is prescribed in daily doses of from two to four grams. It is tasteless and, therefore, can be given to children and such patients whose prostrated condition prevents them from swallowing wafers. It may be administered in wafers, powders, in which case it is taken in some liquid, and finally, in the form of a potion.

Iodoform, which has sometimes been employed as an intestinal antiseptic, is hardly ever used now for this purpose. Salol, in doses

of from 2 to 4 grams, acts particularly upon the stomach; in fact, it is decomposed in the duodenum into carbolic and salicylic acids, which are soon absorbed. This medicine is especially useful when there is reason to believe that infection has invaded the biliary passages, salicylic acid passing into the bile, where its aseptic action is exerted.

Subnitrate or salicylate of bismuth is often combined with the antiseptics above indicated. Salicylate of bismuth is decomposed in the presence of sulphuretted hydrogen originating from intestinal putrefaction; insoluble bismuth sulphide is produced, and the salicylic acid thus liberated is found in the urine, in which it may be detected by means of perchloride of iron. Some authors believe that this offers a very simple means of determining the intensity of digestive putrefactions. Instead of administering through the mouth, antiseptics may be introduced by the rectum. Various medicinal enemas have been favored. Those with carbolic acid were once quite frequently employed.

Although enemas are of service, they have the inconvenience of affecting only the terminal part of the large intestine. On the other hand, the fluid arriving under a certain pressure distends the rectal enlargement, and thus aggravates or maintains certain disorders. Irrigation by means of a soft sound introduced into the colon is free from this disadvantage. Very slight pressure may be employed, so that the liquid flows slowly and, being introduced deeply into the canal, cleansing is more complete. Another advantage of this method is that a large amount of fluid may be circulated. Mild solutions of potassium permanganate are often used (1:10,000) and give very satisfactory results in the treatment of dysentery and dysenteriform enterites. Cantani employed in cholera a fluid containing from 3 to 6 grams of tannin, 30 to 50 grams of gum arabic, and 30 to 50 drops of laudanum per litre (quart). Of course, the formulas may be varied *ad infinitum*. We shall first notice the advantages obtained from intestinal lavage with subnitrate of bismuth. This substance, being deposited upon the mucous membrane, forms a protective layer, and may keep the antiseptic incorporated in contact with the diseased parts. In order to introduce bismuth, which is given in doses of from 10 to 20 grams, it is suspended in quince mucilage or gum arabic water.

In cases of infection of the large intestine we have obtained remarkable results from the use of lavage with peroxide of hydrogen. We

introduce from 50 c.cm. to 100 c.cm. of peroxide of hydrogen, which is rendered alkaline just before use by the addition of a double volume of Vichy water. Peroxide of hydrogen may also be poured into a litre (quart) of boiling water in which should be dissolved 5 grams of sodium chloride, 3 grams of sodium phosphate, and $\frac{1}{2}$ gram of sodium bicarbonate. Peroxide of hydrogen acts as an antiseptic. The oxygen which is liberated hinders the development of the numerous anaërobic microbes inhabiting the intestine and at the same time exercises a very favorable stimulation upon the walls of the digestive canal. This medication is particularly useful in the treatment of colites and notably dysenteriform colites.

Digestive antisepsis is evidently indicated in gastrointestinal infections. An attack of indigestion, seasonal diarrheas, alimentary poisonings, as well as typhoid fever, cholera, and dysentery, are well treated by this medication. In typhoid fever the administration of naphthol or benzonaphthol has the advantage of diminishing toxic manifestations by checking putrefactions. The tongue remains moist, delirium is rare, tympanites less marked, and the fecal matters are almost odorless. As gastrointestinal putrefactions play a considerable rôle in a number of infectious diseases, the use of antiseptics is frequently indicated. In affections of the liver and kidneys, the transformation and elimination of the intestinal poisons being imperfectly effected, it is important to diminish this principal source of intoxication. The same is true of certain cutaneous infections. Prof. Bouchard long ago laid stress upon the excellent effects of intestinal antisepsis in combating acne and furunculosis. Beer yeast probably acts in an analogous manner by regulating the digestive functions.

Antisepsis of the Serous Membranes. Antiseptics, once frequently employed against infections of serous membranes, are no longer used, except in accordance with certain indications. The physician is guided by the course or the bacteriological nature of the effusion. Thus, in pleurisies with the pneumococcus, one or several thoracenteses often suffices. In streptococcic or in pneumococcic pleurisies, which are reproduced repeatedly or are developed within a partition of the pleura, operation for empyema with or without costal resection is resorted to. After the focus is opened it is well to irrigate with a mild antiseptic solution, for example, a 1:1000 solution of corrosive sublimate. The cavity is then washed out with boiled water in order to carry away the antiseptic. In the majority

of cases a single lavage suffices. If, however, the fluid is rapidly reproduced, or it becomes fetid, or the patient presents symptoms due to purulent absorption, antiseptic lavage should again be resorted to. For the same reason these irrigations should always be employed in cases of putrid pleurisies. If the effects of corrosive sublimate are feared a 4 per cent. solution of creolin, a 1 per cent. solution of chloride of zinc, or 1 or 2 per cent. solution of salicylic acid may be used. Not infrequently, however, the practitioner substituting asepsis for antisepsis is contented with lavage with boiled water.

In cases of purulent tubercular pleurisy surgical intervention does not yield very successful results. It has, therefore, been suggested to inject antiseptic solutions into the pleura. Camphorated naphthol particularly has been used in this case.

Interstitial Antisepsis. Interstitial antisepsis may be practised by introducing germicidal fluids into the diseased tissues. The remarkable results obtained by this method in the treatment of malignant pustule are well known. Davaine and Cézard were the first to treat anthrax infection by means of interstitial injections of iodine. They began with 1:4000 solutions and gradually increased to 1 : 400 dilutions. Far more concentrated solutions may easily be employed. The author recommends a mixture of one part of tincture of iodine with one or two parts of iodided water. Fifteen to 20 drops of this liquid are injected into the swollen parts every morning and evening by three or four punctures made around and outside the vesicular zone. The needle is obliquely introduced beneath the skin and the fluid is injected very slowly. The author also makes subcutaneous injections around the congested glands. The treatment is thus continued every day by regulating the amount of the fluid to be introduced according to the general state of the patient and the aspect of the local lesion. The injections should not be suspended until amelioration is well marked, edema is diminished, the skin recovers its suppleness, and fever has disappeared. During and after employment of iodine injections it is well to keep the pustule covered with an antiseptic dressing, such as Van Swieten's solution, mercurial ointment (Cucco), camphorated naphthol, etc. When the eschar separates the part is covered with iodoform. Thus the too rapid development of pyogenic agents and other accidents may be avoided.

Subcutaneous injections of tincture of iodine are well borne, although they are somewhat painful. Some transitory phenomena of

iodism may at times occur under their influence. In one case we observed at the point of several punctures little painful indurations which finally healed at the end of a few weeks without any accident. Russian surgeons have employed for the same purpose a solution of corrosive sublimate. Good results have also been obtained with $1\frac{1}{2}$ per cent. solutions of carbolic acid. This fluid is well borne and gives rise to no disturbance.

It has been suggested to treat erysipelas in the same manner and, in order to arrest its spread, to inject antiseptic fluids at the margin of the inflamed part. In the case of facial erysipelas, however, the evolution seems to us too favorable to necessitate so delicate a method. In erysipelas of the limbs, and especially of the lower extremities, with tendency to diffuse suppuration and sphacelus, the author has several times injected peroxide of hydrogen. He has always utilized the commercial solution diluted with an equal volume of a 4 : 1000 sodium bicarbonate solution. The fluid thus obtained is injected beneath the skin through several punctures in such a manner as to surround the lesion. From 5 to 10 c.cm. of the fluid is thus introduced morning and evening. These injections produce truly marvellous effects, and in several cases they have speedily arrested the invading course of a suppurated or gangrenous lesion.

When a part is attacked by sphacelation and seems irretrievably lost, an attempt may be made to transform it into a harmless mass by a sort of embalmment. This is what Prof. Bouchard realized in a case of gangrene of the lower extremity due to post-typhoidal arteritis. He prescribed injections of a 25 per cent. creosote solution into the diseased limb. The putrefaction was rapidly arrested; the gangrenous member became mummified, and was subsequently eliminated by spontaneous amputation.

General Antisepsis. A last question remains: Is general, at least relative, antisepsis possible? Is it possible to diminish, if not to abolish, the aptitude of the fluids and tissues to microbic invasions?

It is certain that we here encounter great difficulties and that antiseptic substances are too toxic to be administered in amounts responding to this end. In two instances the experiment was made involuntarily: It occurred at the time when carbolized enemas were administered in the treatment of typhoid fever. Inadvertently the mother solution was injected into two patients. Fearful manifestations immediately occurred, but profuse intestinal irrigation practised forthwith succeeded in carrying out the poison. The curious

fact, however, is that the fever fell and did not rise again. The disease was checked, but the fatal dose had nearly been reached.

There is, however, an inoffensive substance which, according to some scientists, renders the organism aseptic. This substance is tannin. The simple injection of this medicine, it is said, suffices to render the blood unfavorable for the development of microbes. It is evidently interesting to resume the study of these phenomena.

While it is hardly possible to realize general antisepsis of the organism against the majority of microbes, we are able, by the use of specifics, to prevent the development of certain determined agents. The medicines described under this name, at least some of them, hinder the multiplication of a given microbe. These are selective antiseptics. At least this has been demonstrated for the salts of quinine in paludism. The germicidal serums act in the same manner, and the facts already known lead us to the hope that we shall see an increase in the list of substances to which certain microbes are so sensitive that minute amounts, in nowise dangerous for the organism, suffice to arrest their development.

Conclusion. If we consider the present tendency of surgeons we find that, after having used and at times abused antiseptics, there is a growing inclination to more and more restrict their employment.

Strong antiseptics are rejected and reserved for certain exceptional cases. On the other hand, asepsis is often substituted for antisepsis by the use of lavage with boiled water. When antiseptics are employed, all those which may produce a caustic action should be eliminated, and it should be borne in mind that germs seem to become rapidly habituated to their germicidal action. It is, therefore, necessary to frequently change the substances employed. Moreover, it is well to remember that an antiseptic often acts as much by stimulating the tissues as by destroying the microbes. The latter are well protected within the organism. They seldom vegetate upon the surface. They penetrate into the folds of the tissues and especially into the glandular crypts, vegetate behind masses of cells, and are thus protected against antiseptics. We must not, therefore, depend too much upon this method, which once seemed so rich in promises, nor must we forget that the best antiseptics are those which are secreted by the organism itself. The efforts of the physician should, therefore, be directed to stimulate the reactions of the system.

Antitoxinic Method.

The antiseptic method intended to destroy germs is related to the antitoxinic method which destroys or neutralizes the poisons. We have already shown that the true antitoxins are those which are secreted by the animal organism in the course or in consequence of infections. There are, however, pharmaceutical substances capable of neutralizing certain microbic poisons. We shall divide them into three groups according as they absorb poisons, precipitate them, or form with them combinations rendering them inoffensive.

The absorption of microbic toxins may be accomplished by means of charcoal powder. This powder fixes not only coloring and odorous substances, but it possesses the power of retaining alkaloids. It was supposed, therefore, especially at the epoch when microbic poisons were believed to be analogous to alkaloids, that the ingestion of charcoal powder would diminish intestinal putrefaction. This is what has in fact taken place. This medication, however, must be supplemented by prescribing a purgative every five or six days, in order to cleanse the intestine of the accumulated charcoal, which is full of toxins.

Albumins and alkaloids are precipitated by certain substances which act upon these two groups of bodies. Such a substance is tannin. It may, therefore, be hoped that this medicine will prove useful in the treatment of microbic intoxications by rendering harmful substances insoluble. In fact, the employment of tannin, tannigen, or tannalbin gives very good results in certain digestive infections. In the course of putrefactions, certain chemically well-defined substances are produced, which may easily be neutralized. Thus, sulphuretted hydrogen, which is so often originated in the intestine, is transformed into an insoluble sulphide by the salts of bismuth. The latter medicine acts not only mechanically, but also as an antitoxic.

It may also be asked whether poisons cannot be neutralized by certain insoluble precipitates which absorb toxins. Evidently the poison is not thus destroyed, and experimentation demonstrates that the combination is not very intimate, since the precipitate acquires noxious properties. Nevertheless, possibly some part of it is neutralized in this manner, which would be a favorable result.

When toxins combine with certain bodies they become less toxic. This is notably what occurs when they come in contact with iodine

and its derivatives. The action of iodine and trichloride of iodine has been well demonstrated by numerous experiments bearing especially upon tetanic and diphtheritic toxins. Probably iodoform acts in the same manner. The latter substance, which is not a strong antiseptic, gives excellent results in the treatment of wounds, because it is decomposed and liberates iodine which, on being generated, unites with toxins and suppresses their action. Carbolic acid seems to act similarly by neutralizing the tetanic toxin. Bacelli has advised the injection of a 2 or 3 per cent. solution of carbolic acid beneath the skin of tetanus patients during twenty days or more. Each injection is to be 3 cg. to 4 cg. Thirty centigrams of carbolic acid is daily introduced in addition to 4 cg. to 6 cg. of morphine. This method counts at present a certain number of successes.

Lastly, if we remember that toxins are destroyed by oxidation, we readily understand the advantages to be derived from oxidizing substances like benzoate of soda. Their administration acts both upon the poisons of the microbes and upon those, by no means less important, which are originated within the organism. These few examples show how interesting it would be to pursue investigations concerning means of neutralizing toxins within the organism.

This antitoxic method, which as yet includes few medicinal substances, assumed great importance after the discoveries of Behring and Kitasato. The majority of medicinal serums are included in this group.

Specific Medication.

Given a disease to find a remedy to cure it is a problem laid down by the ancients. The search for specifics, the preoccupation of which is constantly present in the writings of Pliny, persisted until a recent epoch. The search for specifics, which was nearly abandoned at the time experimentation made us better acquainted with the mode of action of medicines, assumed fresh importance with the discoveries of serumtherapy. The medicinal serum is the specific remedy par excellence. It may be said to be the antidote of the microbic poison. The antidiphtheritic serum, for instance, is the specific medicine of the disease. Its injection causes the pseudomembranes to exfoliate and arrests the symptoms of intoxication. The fact that it has no influence upon identical or analogous pseudomembranes created by other pathogenic agents well demonstrates its specific action. The employment of the serum is not only the best treatment, but also

represents a means of diagnosis. It confirms the old adage: *Naturam morborum curationes ostendunt.*

In the case of a therapeutic serum the medicinal substance represents a product of reaction against a determined toxin. It is, therefore, intelligible that the antitoxin should be special and elective. It is, however, interesting to find in nature vegetable or mineral substances which possess an analogous property and are so decidedly specific that they may equally serve diagnosis and treatment. The specific action is, however, less clear. Although each of these substances cures one disease, they are capable of improving several others, or at least combating certain symptoms.

Aside from therapeutic serums, we are at present acquainted with four specific substances: cinchona, mercury, iodine, and salicylic acid.

Cinchona and Quinine. The febrifuge action of cinchona bark seems to have been observed long ago by the inhabitants of Peru. It was not, however, known in Europe until after the middle of the eighteenth century. The remedy was introduced by the Countess El Cinchon, Vice-queen of Peru, and almost coincidently by the Jesuit missionaries. It was at first known under the designation "Countess' powder" and "Jesuits' powder." In 1679, Louis XIV. bought from the Englishman, Talbot, the secret of a febrifuge remedy which was nothing else than a wine prepared with cinchona bark. It was not until the next century, in 1737, that La Condamine and Joseph of Jussieu determined the cinchona tree. Finally, in 1820, Pelletier and Caventou succeeded in extracting the principal alkaloid of cinchona—quinine.

Cinchona or quinine is not a common antipyretic medicine. It is first of all a specific antipyretic acting upon malarial fevers. The employment of the medicine was regulated by Torti and Sydenham. The method of Torti, which consisted in administering the drug before the paroxysm, was abandoned by its author, who adopted Sydenham's or the English method, the essential principle of which was to give cinchona at the end of the paroxysm. It is known that quinine was abandoned under the influence of Broussais' ideas or was given in insufficient doses, and the fearful reign of malarial fever in the troops of Algeria is not forgotten. At the present day quinine is generally prescribed in one-half to one gram doses. Two or three grams is but exceptionally reached. It should be administered either after the paroxysm or five or six hours before its return. The latter

method is the more usual one. Laveran advises its administration for three days in doses of one-half to one gram (hydrochlorate of quinine), then in doses of 60 cg. to 80 cg. on the eighth, ninth, and tenth days, and a renewal of the same prescription on the fifteenth, sixteenth, twenty-first, and twenty-second days.

Since the researches of Binz it is known that quinine salts exert a harmful action upon amebæ. They are powerless against plants of a low organization, while they rapidly destroy protozoa. By mixing a drop of blood containing hematozoa with a drop of a weak quinine solution we may see how rapidly the movements of the pigmentary grains and the motile filaments are arrested. The fever may recur, because quinine, which kills the adult hematozoa, acts with much less energy upon the encysted germs of these parasites. Thus, quinine represents a specific medicine belonging to the group of germicidal drugs. It is a parasiticide. This is a very important fact, but it would not be safe to generalize the conclusion. It seems probable, however, that such is also the case with mercury—that this substance acts in syphilis as a parasiticide.

Mercury and Iodine. It was not by chance, as has been asserted by Fallope, that mercury was first employed. It had long been praised by the Arabs in the treatment of leprosy. It was in use against parasites, pedicular affections, and the itches. It was tried in syphilis by analogy. Employed for the first time by Wichmann in 1497, it was particularly praised by Berenger (of Carpi) and Jean de Vigo, who prescribed it in the form of plasters; by Fracaster, who employed it in friction, and by Matthioli, who administered it internally. At present mercury is administered by the digestive canal or by inunctions, by subcutaneous or intramuscular injection, and, in grave cases, by intravenous injection. We may employ metallic mercury (blue pill, Sedillot's pills, inunctions with Neapolitan unguentum, injections of mercury, etc.), the insoluble salts (pill of protoiodide, injections of calomel), the soluble salts, notably corrosive sublimate (Dupuytren's pills, Van Swieten's solution), biniodide (biniodized oils), peptonate, benzoate, and cyanide. The soluble salts are, of course, used for intravenous injection. Sometimes corrosive sublimate is employed in doses of 1 mg. to 8 mg.; oftener cyanide of mercury.

The powerful antiseptic properties of mercury salts lead to the presumption that this medicine acts upon the pathogenic agents of syphilis. Direct experimentation being impracticable, hypotheses

have been advanced. It is well to notice, however, that the question is undoubtedly one of specific action, for mercury does not act similarly against other infections. On the other hand, it is not equally useful against all syphilitic manifestations. In the primary stage mercury acts upon the chancre and adenites. Its action is still more marked upon the secondary manifestations. General treatment makes them disappear; local treatment often suffices to cure them.

We must recognize, however, that the specific action of mercury is not perfect. Certain manifestations are but slightly modified under its influence. The generalized disturbances of the secondary period, syphilitic fever, syphilitic anemia, pseudochlorosis, and secondary cephalalgia frequently resist its action. Likewise, more profound manifestations, tubercular and pustular syphilides, and precocious gummata require complementary treatment. Finally, at a late period, mercury is insufficient. In all such cases recourse should be had to another specific, advised for the first time in 1836 by Wallace (of Dublin), and the indications for which have been well regulated by Ricor. We refer to iodine in the form of iodide of potassium. Thus we have two specifics for one disease, and, a fact of particular interest, each of these substances has its peculiar indications, so that they must be employed successively or in conjunction, as the case may be.

The iodide is not infallible. There are cases on record in which treatment regularly followed produced no effect. The author observed a young man suffering from an indurated chancre. Being the relative of a very distinguished physician, he was treated from the very beginning and submitted to mercurial medication. Two years later he suffered from ocular disorders. One of the ablest ophthalmologists of Paris prescribed the mixed treatment for him. Instead of the improvement expected from an energetic treatment, symptoms of spinal syphilis made their appearance. In spite of all the medication employed, in spite of the iodides, in spite of mercury injected in the form of cyanide into the veins, the paralysis followed an ascending course, and terminated fatally with the appearance of bulbar phenomena. Facts of this kind are rare, but are not altogether exceptional. In the presence of them doubt has been expressed as to the efficiency of mercury and potassium iodide. The doubt is not well founded. Treatments, even when specific, do not always succeed. Clinical phenomena are too complex to be covered by a single formula explaining their entire evolution. Deaths occur

from syphilis in spite of mercury and iodide, as people die from diphtheria in spite of antidiphtheritic serum. We have reason to be highly satisfied that it is possible to cure the great majority of sufferers.

It is hardly necessary to say that specific treatment has no action upon the common lesions consecutive to syphilitic lesions. Although it may still improve certain scleroses, it is evidently incapable of removing lesions produced by stricture or obliteration of arteries, fibrous cicatrices, and foci of softening.

We need not dwell at length upon the necessity of having two specifics for one disease. One hypothesis alone seems plausible. It may be admitted that the agent of syphilis undergoes profound modifications within the organism which it has invaded. Although very virulent in the beginning, as is evident from the contagiousness of the primary and secondary manifestations, the agent gives rise only to superficial lesions. Later it possesses very slight, if any, virulence, and yet at this period of its evolution it seems to be more dangerous for the organism. It becomes localized at various points and produces reactions unlike those of the former periods. There seems to be no apparent analogy between a papular syphilide and a gumma. The reason the reactions of the organism which produce the lesion are so dissimilar is evidently that the parasite is modified or that the organism, being gradually impregnated with the toxins, has undergone a profound transformation. In the two cases, the manifestations being no longer analogous, the necessity of two different treatments is readily conceivable.

We must here recall that iodine is not a specific for syphilis alone. Without speaking of its action upon scrofulosis, there is another infection in which iodine is a specific, namely, actinomycosis. Thomasses, of Utrecht, was the first to show that potassium iodide may cure actinomycosis in animals. Nocard made it known in France. Then successful attempts were made in man by Van Hersen and others. Netter, Duguet, and Ducor have reported interesting observations. The favorable effects usually become manifest when phenomena of iodism appear.

Salicylic Acid. Salicylic acid and its derivatives are often spoken of as specifics for acute articular rheumatism.

Maclagan tried salicin in 1874. He started from the idea that the willow, growing in damp countries, where rheumatism is frequent, must contain some antirheumatic substance, since cinchona, which

grows in malarial countries, contains a febrifuge substance. Buss called attention to salicylic acid. Stricker showed the good effects of the substance (1876), for which Senator substituted salicylate of soda. At present the last-named medicine and certain similar substances, such as salol, salipyrine, salophen, and aspirin, are employed. Methyl salicylate is used for external applications.

All these preparations give excellent results. Are they, however, true specific medicaments? A great many authorities so believe, and argue that those arthrites which resist the action of the medicine are not truly rheumatic. In fact, it is certain that the arthropathies of secondary infections, notably gonorrheal arthropathies, are not benefited by salicylates as are the arthropathies of acute articular rheumatism. This is an argument in support of the specific character. It has been objected that the visceral manifestations occurring in the course of their evolution are not modified, but we have seen analogous results in many other cases. Specific serums are likewise powerless to remedy certain visceral evolutions, such as nephritis and paralyses. We may, therefore, class the salicylates among the specific medicines, although it must be acknowledged that we are completely ignorant of their mode of action.

If we now consider the four specific medicines, we see that one of them—quinine—acts as a parasiticide, and that the other three possess an influence the mechanism of which remains unknown.

Bacteriotherapy.

Bacteriotherapy is a therapeutic method aiming to combat infection by infection, viz., to introduce virulent agents or microbic toxins into the diseased organism.

It has been long known to clinical observers that erysipelas may cause torpid infectious lesions to retrocede and disappear. Ulcers, lupus, syphilitic lesions, and cancer have been seen to improve and heal under the influence of an intercurrent erysipelas. It may, therefore, be questioned whether, in certain cases, it would not be advisable to inoculate disease for therapeutic purposes. Ricor made the first attempt of this kind in syphilis. The method proved unsuccessful, and experiments of this nature have only recently been taken up. Following Fehleisen, several physicians injected cultures of living and virulent streptococcus into patients suffering from cancer. The procedure was a dangerous one. Several of the patients thus treated succumbed. Nevertheless, inoculation of

virulent products is still employed in one case, namely, in the treatment of pannus; the introduction of gonorrheal pus induces a purulent conjunctivitis which is sometimes followed by a cure.

While virulent microbes are dangerous, non-pathogenic microbes may be introduced with apparent safety. An attempt has been made to treat tuberculosis by inhalations of the bacterium termo. The results were negative, and the procedure was abandoned. A therapeutic measure has recently been resorted to which enters the domain of bacteriotherapy. We refer to the ingestion of beer yeast against suppurative cutaneous inflammations and notably furunculosis.

This method, which was indicated as early as 1852 by an English physician, Mosse, is a popular remedy in the north of France. It has been employed by Debouzy, Gobert, and De Backer. It is only since the work of Dr. Brocq, however, that attention has been drawn to this subject. The investigations of this author show that by giving to a patient one teaspoonful of fresh yeast three times a day we may arrest the development of furuncles, suppress pain, and hasten cicatrization. It is not exactly known how the yeast acts. It probably produces its effect by regulating digestion, which is so often disturbed in these patients.

The employment of living microbes for therapeutic purposes seems to have a rather restricted field. As microbes do not act except by their soluble products, it may be questioned whether toxins might not render the same therapeutic service. We must consider two quite different cases. We may combat an infection by means of products originated by microbes different from the one which we wish to antagonize. On the other hand, we may employ the toxins secreted by the pathogenic microbe which we wish to attack. The former method is very much like bacteriotherapy, which has already been studied. There are some experiments in its support. When speaking of microbic associations we alluded to the fact that pyocyaneus toxins hinder the evolution of anthrax. Sterilized cultures of the bacillus prodigiosus act in the same manner, at least in rabbits. Kostiurine and Krainski have shown that putrefied fluids combat anthrax and tuberculosis. Therapeutic attempts were made on man. Rumpf and Kraus have treated typhoid cases by sterilized cultures of the bacillus pyocyaneus.

Streptococcic Toxinotherapy. Cultures of the streptococcus have been the subject of the greatest number of researches. Lassar,

Spronck, Coley, Friedreich, Kocher, and Répin treated a certain number of neoplasms by means of streptococcic toxins and obtained a few successes, especially in cases of sarcomata. The procedures employed by these various observers were not, however, always the same.

Lassar,[1] fearing the use of simply filtered cultures, the high toxicity of which we have proved as regards animals, resorted to cultures sterilized by heat and freed from all figurate elements by means of filtration through porcelain. The greatest part of the noxious substances is thus destroyed, and the fluid is not toxic unless it is derived from an extremely virulent culture. Taking ground upon the same experimental facts, Spronck[2] also tried the heated cultures. Believing, however, that the toxic substances would be more active from a therapeutic standpoint, he employed a mixture of heated and simply filtered cultures. Répin[3] employed filtered but not heated cultures. Finally, Coley,[4] inspired by our investigations on microbic associations, utilized a mixture of streptococcic toxins and sterilized cultures of the bacillus prodigiosus. Not only the composition of the fluid, but also the mode of injection varied. While Lassar and Coley injected the toxins into the interior of the tumors, Spronck and Répin injected them at a distant point, and Répin finally introduced them into the veins. These various procedures having given a few successes in the treatment of neoplasms, we, with Dr. Hallopeau,[5] pursued analogous researches upon lupus. It seemed to us, however, that our first duty was to begin with harmless fluids—*i. e.*, to try streptococcic cultures sterilized by heat.

We operated in the following manner: Bouillon containing a streptococcus of medium virulence was kept in the incubator for fifteen days. At the end of this period the culture was evaporated and reduced to one-sixth of its original volume, then heated in the autoclave to 230° F. (110° C.) for fifteen hours. The culture was not filtered, in order that we might use both the toxins modified by heat

[1] Lassar. Zur Erysipelimpfung. Deutsche med. Wochenschrift, 1891, No. 29.

[2] Spronck. Tumeurs malignes et maladies infectieuses. Annales de l'Institut Pasteur, 1892, p. 683.

[3] Répin. La toxithérapie des tumeurs malignes. Revue de chirurgie, June, 1895, p. 465.

[4] Coley. Treatment of Inoperable Malignant Tumors with the Toxin of Erysipelas and the Bacillus Prodigiosus. American Journal of the Medical Sciences, July, 1894.

[5] Hallopeau and Roger. Action des toxines streptococciques sur le lupus. La presse médicale, April 8, 1896.

and the microbic cadavers. The fluid thus obtained is almost inoffensive. Guinea-pigs, rabbits, and mules received considerable amounts without presenting any notable disturbance. We kept for two years a rabbit which had received 400 c.cm. of sterilized streptococcic toxins and which continued in good health. It seemed, therefore, that the fluids were not apt to give rise at the end of a certain period of time to any organic disturbances or visceral lesions. The only phenomena produced in the animals by subcutaneous injections were tumefaction at the point inoculated and sometimes a transitory rise in temperature. There are some exceptions, however, to this rule. An animal may manifest an active reaction, while other animals present no disorder whatever. We observed a mule in which each injection of the toxin produced fever, profuse sweating, and lassitude, while other mules similarly inoculated showed no reaction. The same individual peculiarities are more markedly observed when man is experimented upon.

Our therapeutic inoculations, which were practised upon seven women, were all made into the diseased regions, beneath the skin. We began by injecting five or six drops of the fluid, representing thirty to thirty-six drops of the primary culture; then, if the sensitiveness of the patient was not too great, we gradually increased the dosage. We finally introduced as many as thirty drops of toxins at one sitting, about 9 c.cm. of the culture. The injection generally caused a sufficiently strong local reaction. An edematous tumefaction, a true fluxion, was generally produced, which set in from fifteen minutes to two or three hours after the injection. The edema was in some cases sufficiently intense to disturb the patient and notably to cause closure of the eyelids, or to embarass movement of the lips. At the end of a few hours, however, the symptoms improved, and within a day or two the edema disappeared altogether. These local manifestations evidently vary according to the amount introduced. Individual predisposition, however, seems to play the principal rôle in their production. In one of our patients the smallest injection gave rise to tumefactions which, at first, seemed quite disquieting. In spite of the local disorders, the general phenomena were not very pronounced. A few patients complained of malaise and lassitude, several of lumbar pains for a day or two. Contrary to what has been noted by other observers, however, we noticed no veritable fever. The temperature, carefully taken every hour, did not rise above 99.5° F. (37.5° C.). Only once a patient

developed a temperature of 104° F. (40° C.). The interesting fact in this case was that the hyperthermia was produced at the end of two months of treatment, while previous injections of practically the same amounts had given rise to no fever, nor did subsequent inoculations.

It did not seem to us that a well-marked habit to the toxins was produced. The local phenomena were nearly always the same in the same patient. In the woman who presented such a remarkable susceptibility the reactional swelling was produced at the end of nine months of treatment just as on the first day. This result, which differs notably from that obtained by other experimenters, is due, perhaps, to the presence of microbic cadavers in the liquid employed, perhaps to the relatively long interval between the injections; in fact, the latter were given only once a week.

The action of sterilized cultures of the bacillus prodigiosus was quite different. This microbe was cultivated in bouillon, then, at the end of eight days, the culture was sterilized at a temperature of 230° F. (110° C.) for ten minutes and injected without being filtered. The fluid thus prepared, mixed with the streptococcic culture, was tried on four patients. We began by introducing three drops of the culture of bacillus prodigiosus. This minute dose caused accidents which somewhat alarmed us, at least with regard to two of the patients. Three hours after the injection violent chills occurred, the extremities became cold, the pulse was weak and rapid, the central temperature rose to 102.2° F. and to 103.1° F. (39° and 39.5° C.); these symptoms were followed by nausea, vomiting and, in one of the patients, diarrhea with incontinence of feces. These disorders, however, were only transitory. On the following day the patients simply felt tired. The crisis terminated in a very profuse herpes labialis. Instructed by these results, we introduced only two drops of the culture for the second injection. The symptoms consisted in a slight malaise and an insignificant rise in temperature. Subsequently the patients became habituated to the toxin, and received progressively increasing doses—as many as six drops—without presenting any appreciable reactions.

The action of the *bacillus prodigiosus* demonstrated far better than all laboratory experiments that a minute dose of toxin may give rise to extremely grave general manifestations, and clearly establishes the toxi-infectious origin of herpes. Lastly, it is very interesting to note that the soluble products of the bacillus pro-

digiosus and non-pathogenic microbes proved far more toxic than those of the streptococcus. The differences were very remarkable. Three drops of the bacillus prodigiosus produced disquieting symptoms, while thirty drops of a streptococcic culture, representing 9 c.cm. of the primary culture, produced only a local reaction. Sterilization, however, had been made according to the same procedure, viz., by heat at 210° F. (110° C.).

If now we consider the results obtained in our seven patients we find that in one lupus was completely cured. In two a very marked improvement was produced; in the other four, amelioration was slight or *nil*. The best results were obtained in young subjects, whose vital reaction is more energetic and more readily aroused, and in those whose lupuses were characterized by fungous, vegetating tubercles and deep and extensive ulceration. Under the influence of the treatment the tubercles were reduced, the discharges disappeared, and the ulcerations rapidly diminished. Finally, there was produced a cicatrix remarkable for its perfect elasticity; it was almost normal skin. On the other hand, the result was slight or negative in those cases in which sclerosis dominated and the tubercles were embedded in cicatricial tissues. All that was observed in such patients was a reduction in the size of the tubercles and disappearance of a few.

The results obtained by us will, perhaps, not appear very encouraging. The patients, however, manifested great enthusiasm with regard to these therapeutic attempts. In despair at the failure of other methods, the sufferers were satisfied with the amelioration obtained at our hands. The reason we did not further pursue our attempts is that microbic toxins are such actively energetic substances that one cannot exercise too much prudence when applying them to human therapeutics. We would not have made even the attempts above reported had we not been led to do so by laboratory investigations and by results obtained in the treatment of cancer. At all events, we watched the patients with the greatest care. We repeatedly examined their urine and we prolonged the experiment because we noticed no permanent disorder and no albuminuria. The results obtained did not seem to us, however, sufficiently satisfactory for continuing our therapeutic attempts. Nevertheless, we thought it might be of value to make known our researches in the hope that, if taken up by others with some technical modifications, they would lead to a better method. The method should be so

modified as to increase the local action and to suppress the general manifestations. In fact, it seems that the toxins act by the inflammation induced by them; and it is for this reason that we injected them into the diseased tissue itself. What proves that we were right in so doing is the fact that in a case of bilateral lupus the inoculated side rapidly improved, while the opposite side presented but slight modification. Moreover, for fear of accidents, we made only one injection per week. It is better to make one every two or three days. Lastly, our observations showed that the addition of soluble products of the bacillus prodigiosus render the fluids much more efficacious. In a case in which the streptococcic toxins were employed alone the results were almost *nil*. Each injection however, produced very marked edema in the patient. For this reason we did not add the bacillus prodigiosus, and noted that fluxions caused by the streptococcus alone were not sufficient to ameliorate lupus. Likewise, in the patient who recovered and in those who notably improved, the favorable effects were not very clear until after the mixture of the two toxins was employed.

It is not, however, to be concluded that these microbic products possess specific germicidal power. The toxins probably act not upon the bacillus, but upon the organism. They stimulate the responsive activity of the economy and attract to the diseased spot serum and leucocytes which combat the bacilli and the morbid tissue developed under their influence.

While the results obtained are not sufficiently successful to warrant a systematic continuance of the bacteriotherapic method, it would be reasonable to try it in certain suitable cases, viz., in young persons suffering from fungus and ulcerating forms of lupus. We are aware that cases of this variety are most frequently cured by classical procedures. When, however, the latter fail, a last attempt may be made by means of the toxins. It is well to repeat that it is necessary to increase the therapeutic effects by practising the injections at shorter intervals and by employing more active fluids, or by making use of a serum analogous to that which was employed by Emmerich and Scholl in the treatment of cancer.

Streptococcic Hematoxin. Instead of a culture, Emmerich and Scholl employed the serum of infected animals. One might suppose, in fact, that active toxins would be found therein in greater abundance.

The serum of sheep infected with the streptococcus was filtered

through porcelain in order to free it from all living elements. This serum was injected into neoplasms in doses varying from 1 c.cm to 25 c.cm. The injections produced at the point of inoculation a redness analogous to that of erysipelas, which persisted for a day or two. A febrile movement was at the same time observed. It is to be noted that the more intense the local reactions the better were the effects produced. Such is precisely the case when sterilized cultures are made use of. The serum proved inefficient in only two cases. In the other patients the more recent the tumor the greater was the activity of the serum. Its employment is advisable in cases of postoperative relapses.

The report of Emmerich and Scholl was too important not to immediately give rise to control researches. Unfortunately, the results obtained by other experimenters were not confirmative. Some of them, Schuler among others, reported successes, but the majority of physicians obtained no appreciable results, and some of them even observed accidents. Burns found the patients feverish and dyspneic, the heart weakened and the urine albuminous. In spite of the answers given by Emmerich and Scholl to criticisms, their method is to-day abandoned. It does not seem to be superior to bacteriotherapy, and it has the disadvantage of being more complicated and, what is of greater consequence, more dangerous.

Tuberculin. The method that consists in treating an infection by the soluble products engendered by the pathogenic agent which is to be combated differs considerably from the toxinotherapic procedure above studied. The latter is based upon experimental data; such is not the case with the former. In fact, numerous investigations have demonstrated that microbic products favor the development of the microbe which has secreted them. Although they are often endowed with vaccinating power, they are never curative. Perhaps it will some day be possible to prepare a substance possessing therapeutic properties by modifying these products. This is what Smirnow claims to have obtained by subjecting diphtheritic toxin to electrolysis.

Microbic products have been utilized in the treatment of three diseases—tuberculosis, glanders, and typhoid fever.

The enthusiasm with which the first communication of Koch was met is well remembered. At the Berlin Congress of 1890 the eminent scientist announced that he had succeeded in arresting the evolution of tuberculosis in animals by means of a product which was called

tuberculin or Koch's "lymph." It can be prepared by reducing to one-tenth of its volume a culture of tubercle bacilli developed in glycerinated peptonized veal bouillon. When filtered through porcelain it is obtained in the form of a limpid and brownish fluid, the composition of which is evidently quite variable. Hence, it should not be employed except after its action has been verified upon tubercular guinea-pigs.

Like other microbic products, tuberculin acts only when it is injected beneath the skin or into the veins. When introduced by the alimentary canal it has no effect. Its action is not very marked upon animals; a guinea-pig easily resists 2 c.cm. of the "lymph," while a dose of 0.25 c.cm. produces notable effects in man. By reducing the results to the same unit of weight, it may be seen that man is from 1000 to 1500 times more sensitive to this remedy than the guinea-pig. Therefore, the action of tuberculin should be studied upon man. Koch had the courage to experiment upon himself. He injected 0.25 c.cm. of the "lymph" into his arm. Three or four hours later he experienced twitchings in his limbs and paroxysms of coughing; later on, chills, nausea, vomiting, and fever attaining 102.2° F. (39° C.). At the end of twelve hours the morbid phenomena disappeared, except a slight tired feeling.

In a healthy man or in individuals suffering from a non-tubercular affection, it is necessary to employ at least 0.01 c.cm. of lymph in order to produce disturbances. The temperature rises to 100.4° F. (38° C.). In tuberculous subjects 0.003 c.cm. and even 0.002 c.cm. suffices to arouse intense reactions.

In his first communication Koch reports an experiment which seems to have been the point of departure of his investigations. He asserted, contrary to Dr. Arloing, that, in a tubercular guinea-pig, a reinoculation of the virus gives rise to only slight lesions without any tendency to generalization. It would be inferred from this fact that a first inoculation confers a certain degree of immunity. Hence it was natural to investigate whether the soluble products of the tubercle bacillus, like those of a great number of bacteria, would not act in the same manner. Koch claimed to have obtained this result, but he indicated it only incidentally without relating any experiment. Arloing, Rodet, and Courmont took up the question. They pursued a great number of researches on this subject and constantly failed. The animals were never rendered immune; on the contrary, at times they manifested a morbid receptivity and succumbed more rapidly

than the controls. The same failure attended the experiments of Jaccoud, Dujardin-Beaumetz, and Dubief. It may, therefore, be said that, with respect to this second point, Koch's tuberculin failed to realize what had been promised by its inventor.

The question of greater consequence is, however, the therapeutic action of the lymph. In this regard, Koch teaches us that small amounts of the lymph are capable of killing tubercular guinea-pigs, while, by diminishing the doses, it is possible to cause reactions followed by a notable amelioration. Are the guinea-pigs cured, however? How long do they survive? What happens as a result of these injections? May not these injections cause grave and tardily supervening accidents, as the experiments of Maffucci tend to show? These are questions requiring answers. Such information is indispensable before the application to man of a remedy so active and so dangerous.

According to Koch, the lymph is to be used for therapeutic purposes in the following manner: In cases of pulmonary tuberculosis very small doses should be injected at first; in fortunate cases amelioration is rapidly produced. Cough diminishes, the expectoration assumes a mucous character, the general state is improved, the bacilli decrease and finally disappear. This result may be obtained in four or six weeks, at least, in patients suffering from the first stage of the disease. According to Koch, such patients can certainly be cured. Even, however, when the disease has reached the stage of excavation and the lung is invaded by innumerable pyogenic microbes, the treatment may still produce some amelioration.

By studying more closely the modifications occurring in tubercular foci it may be seen that the lymph acts upon the tissues, provided the latter be yet living and impregnated with toxin. The bacilli are not reached and are simply rejected with the neighboring parts. Be that as it may, the chief action of the lymph is upon the tissues surrounding the tubercles, and the mechanism of this action was demonstrated by Bouchard's experiments. This author found that tuberculin acts by exciting the vasodilator centre. If the fundus of the eye of the rabbit, into which this substance has been injected, is examined an active dilatation of the vessels is observed (hence the name ectasin, given by Bouchard to the lymph). This dilatation persists for several hours. If, however, a vasoconstrictor substance or *anectasin* (for example, the sterilized culture of the bacillus pyocyaneus) be injected into a rabbit thus prepared the papilla becomes

anemic; then, at the end of half an hour, the action of the anectasin having ceased, that of ectasin is again manifested and the vessels dilate. The same phenomena occur around those tubercular foci which, in consequence of the vasomotor dilatation, are the seat of a profuse exudation of serosity and of an active diapedesis (Kromeyer, Cornil). The neoplastic tissue resists, or it is secondarily affected (coagulation necrosis, suppuration, fatty degeneration) and may be eliminated. In the case of an ulceration occupying a mucous membrane, it becomes transformed into a simple wound and covered with granulations of a benign nature (Jürgens). Moreover, Koch has remarked that successive injections arouse less and less violent reactions. In his opinion this result is not due to the formation of habit, but to the progressive disappearance of diseased tissues. When all the neoplasms are eliminated, reaction becomes similar to that which is presented by a healthy individual. Let us note, however, that in certain cases the sensitiveness of the patient increases with each new inoculation. In other instances, habit is established long before the elimination of the diseased parts.

Before considering the results obtained by various physicians who have experimented with tuberculin, we must briefly indicate the principal dangers to which this medicine exposes the subjects.

These dangers are at times dependent upon a general intoxication; at times upon a too intense local reaction. Thus, as regards the respiratory apparatus, pulmonary edema and edema of the glottis (which has in some cases proved fatal by suffocation), hemoptysis, pleural effusions, and bronchopneumonias have been observed. In other cases auscultation has revealed an aggravation of the physical signs connected with the pulmonary lesions, which have sometimes caused death. Virchow has dwelt upon these lesions, which he designated as "injection pneumonia," and which consist essentially of a phlegmonous process which causes rapid destruction resulting in pulmonary excavations. Coincidently, new small tubercles appear, which are due to a "mobilization" of the bacilli. A more or less torpid tuberculosis may thus rapidly terminate by generalization of the infection and development of an acute miliary tuberculosis. Experimenters who have studied the action of therapeutic doses of the lymph in tubercular guinea-pigs have often observed similar effects. In this connection, nothing is more instructive than the researches of Arloing and his collaborators. The lymph hastened generalization, and at times it caused this condition in animals

inoculated with an attenuated virus which produced only local lesions.

Intense visceral congestions are found at the necropsy of animals killed by tuberculin injections. The same phenomena are observed in man. Thus, there are on record hemorrhagic nephrites, renal congestions, expressed by albuminuria or hematuria. In a case of Rosenbach's the patient suffered from an almost complete anuria; in twenty-four hours he voided 50 c.cm. of urine of a mahogany color, which was transformed into a solid mass by the addition of nitric acid. In children suffering from tubercular meningitis the use of the lymph gave rise to acute edema of the meninges, which hastened the fatal termination. Lastly, under the influence of this medicine, intestinal ulcerations have been seen to end in perforation.

Among the manifestations ascribable to a general intoxication some are devoid of gravity. Such are various eruptions, leucocytosis, albuminuria, urobilinuria (Cavallero), and peptonuria; the last symptom is surely due to the medicine itself, since it has been observed in healthy individuals (Kahler), or in normal animals (Bouchard). In other cases the phenomena are more serious. Transitory delirium or even permanent psychoses occur (Jolly). Angina pectoris, loss of consciousness, coma, and, finally, a tendency to cardiac collapse with cyanosis, cold extremities, weak and irregular pulse may supervene. Even permanent lesions of the endocardium may occur (Hallopeau).

The remedy is well borne only in those cases in which the alterations are superficial and the mortified tissues can easily be eliminated. In fact, accidents are rarer when the lymph is employed against cutaneous tuberculosis or tuberculosis of the conjunctiva, nose, mouth, and intestine. Its action on the larynx must be very carefully watched. Finally, as regards the lungs, it may be employed only when the lesions are not far advanced or when the cavities communicate largely with the bronchi. It is well to remark that if the diseased tissues cannot be eliminated by expectoration no favorable results can ever be obtained. In cases of articular tuberculosis Prof. Cornil observed enormous painful swelling in the diseased joints. At the end of a certain period of time these manifestations improved, but there was no amelioration of the disease. On the other hand, good results were obtained in a few cases in which surgical intervention was resorted to.

Are the dangers accompanying injection of the lymph compensated by the benefits derived by the patient? At present this question can be answered in a decisive manner. Even in external tuberculoses, amelioration, when any has occurred, has been mostly relative and transitory. In cases of lupus—*i. e.*, in instances in which the best results are obtained—only the superficial nodules are eliminated; the deep-seated ones persist, and the patients soon cease to present any more reaction at the diseased point, even when doses of 0.08 c.cm. are employed. In this connection, nothing is as instructive as the perusal of the report prepared by Dr. Besnier in the name of the St. Louis Hospital Commission. It regards the treatment of thirty-eight cases of lupus. Improvement frequently occurred, especially in the open forms of the disease, but this improvement was not permanent, and the affection resumed its course. At times it was aggravated. Thus, even in cases of attenuated tuberculoses, Koch's treatment is often inefficient. In other cases it may prove dangerous. The use of the lymph was therefore gradually abandoned.

It would, however, be unjust to wholly condemn the method. Although tuberculin, taken as a whole, is more harmful than otherwise, it may be hoped that it will some day be possible to separate the curative substances contained in it. This is what Koch, with the assistance of Proskauer and Brieger, has attempted. The substance which he obtained, however, produces the same dangerous effects as the raw tuberculin, and is no more to be recommended than the former. W. Hunter announced in the London Congress of 1895 that he had isolated from tuberculin three active substances: the first one, of an albuminoid nature, is hyperthermizing; the other two are albumoses, one of which possesses a phlogogenic power, the other exerts a curative action. Klebs, Kuhne, and Röhmer have pursued similar researches.

In a more recent communication Koch indicated a new preparation of tuberculin: The desiccated bacilli are triturated in an agate mortar with a pestle of the same substance. The magma is taken with a little water and is centrifuged for thirty to thirty-five minutes. The fluid obtained is tuberculin O, which is analogous to the old raw tuberculin. It possesses no therapeutic properties. The residue is then taken, dried, and again triturated, and, after having added water to it, is again centrifuged. When this operation has been repeated several times almost all the precipitate is exhausted and a series of

fluids obtained which are mixed together. Thus is obtained tuberculin R, which, unlike tuberculin O, contains substances insoluble in glycerin. This new tuberculin is germicidal, it causes no abscesses, and possesses immunizing and curative properties. No febrile reaction is said to occur.[1]

The first control researches due to Letulle and Péron[2] have hardly been favorable to the method. Its only advantage is that it is not dangerous.[3] Judging, however, by the small number of facts thus far published, it does not seem that we as yet possess the specific remedy of tuberculosis.

Mallein. The discovery of tuberculin led bacteriologists to look for analogous substances in other cultures. Thus, Helman and Kalning prepared a substance, mallein. This product is hardly ever used for any other than diagnostic purposes. According to Bonome and Vivaldi, even minute doses cause death in cats suffering from glanders, while they produce amelioration in guinea-pigs, rabbits, and man. As to the horse, numerous experiments seem to demonstrate that mallein may favor cicatrization and at times bring about a recovery, at least when the lesions are recent and discrete.

A last attempt was made with reference to typhoid fever. E. Fraenkel treated patients with sterilized cultures of Eberth's bacillus. The first effect is a rise in the temperature, followed by an at least temporary fall. The statistics published by the author seem quite encouraging.

Serumtherapy.

The discovery of serumtherapy, the way to which was prepared by the researches on the germicidal properties of the fluids of the organism and by the efforts of experimental therapeutics, due to Drs. Richet and Héricourt, belongs, as is known, to Behring and Kitasato. Having recognized that the serum of animals vaccinated against diphtheria is antitoxic they were led to employ it for therapeutic purposes.

After the data reported in the preceding chapter we may readily comprehend the radical difference separating bacteriotherapy from

[1] Koch. Ueber neue Tuberkulin Praeparate. Deutsche med. Wochenschrift, August 1, 1897.

[2] Letulle and Péron. La nouvelle tuberculine de Koch. La presse médicale, August 21, 1897.

[3] Borquier. La nouvelle tuberculine R et son emploi, en particulier dans la tuberculose pulmonaire. Thèse de Paris, 1897.

serumtherapy. The aim of the former method is to act with the products secreted by microbes, that of the second is to discover in the blood not what remains of the toxins introduced, but the principles which are developed under its influence. Serumtherapy employs materials elaborated by the organism itself in its defense against infection. It is therapeutic and vaccinating alike, but the immunity which it confers is a *passive immunity.* The organism takes no part in its production; it makes no effort; it simply allows itself to be impregnated by the substances introduced. On the other hand, bacteriotherapy is oftener preventive than curative. It produces immunity, but by means of an altogether different mechanism. It is a process of *active immunity* dependent upon an effort of the organism.

Choice of the Animal. It was formerly believed that the more sensitive the organism was to the disease the better it reacted. This idea led authors to vaccinate the most susceptible animals. At present it seems to be demonstrated that, although the law is real, it is subject to numerous exceptions and that it is possible to confer active immunity whether the animals are naturally refractory or not. We have proof of this in what occurs in diphtheria. Behring believed that an animal sensitive to the virus should be employed, and he experimented upon sheep. Roux has shown that the horse, which is only slightly susceptible to diphtheria, gives just as efficacious a serum. The same is true of tetanus; Roux and Vaillard have demonstrated that the chicken, which does not contract this infection, furnishes a therapeutic serum when large amounts of toxins are injected into it.

It is not so much the degree of sensitiveness or natural resistance of the animal as the possibility of easily obtaining large quantities of blood and a serum devoid of toxic properties that must guide us in our choice. In fact, it is known that transfusion between individuals of different species is not always inoffensive. Experimentation cannot, however, furnish decisive data to therapeutics, for the toxicity of the serum of a given species varies considerably, according to the species into which it is injected. It is, therefore, impossible to know with sufficient accuracy what its effect would be in man. Nevertheless, it is interesting to look for the solution of the problem in animals.

By making intravenous injections of various serums into rabbits, the following results have been obtained:

Animal Furnishing the Serum.	*Fatal Dose for One Kilogram of Rabbit.*
Cattle	8 c.cm. (Rummo and Bordoni).
Sheep	12 c.cm. (Rummo and Bordoni).
Calf	13 c.cm. (Rummo and Bordoni).
Man	15 c.cm. (Mairet and Bose).
Chicken	20 c.cm. (Rummo and Bordoni).
Horse	80 c.cm. (Zagari).

Clinical facts seem to be in harmony with the data of experimentation for establishing that the serum of the dog is not well borne, while that of the horse is excellent, and may be employed in large doses. The serum of the cow, which is very toxic for the rabbit, is very slightly so for man. In the treatment of variola Dr. Béclère injected as much as 1560 c.cm. without giving rise to any disturbance. Finally, it is certain that the serum of man would be the best from this standpoint. It will be shown later on that it has been employed in therapeutics in exceptional cases.

Vaccination of Animals. The animal being chosen, the reactions of its organism must be called into play in order to increase its resistance. This may be realized by three methods:

1. Inoculation of living microbes.
2. Injection of toxins produced in artificial cultures.
3. Injection of toxins derived from the diseased organism.

The first procedure exposes to certain accidents. After injection of living cultures into animals the microbes may persist in the blood, even when the subject seems to have recovered. For instance, the antistreptococcic serum derived from animals prepared by means of living cultures has sometimes caused phlegmonous erysipelas, because it still contained streptococci which were undoubtedly attenuated, but nevertheless capable of producing local lesions.

Of course, this danger may be avoided by employing sterilized cultures, modified or not by physical or chemical agents. There is no doubt that immunity thus created is much less durable than when it results from virulent inoculations. However, it then suffices to repeat the injections of toxins for maintaining or increasing the properties of the serum, for it is to be noted in this connection that repeated injections of small doses are more efficient than the introduction of a single, even though greater, amount (Roux and Metchnikoff).

The animals vaccinated by means of soluble substances have already been employed for the preparation of a great number of serums. It is quite evident that serums may be obtained against

all the known pathogenic agents, on condition, however, that a method of vaccination can be found. For example, the reason attempts failed in tuberculosis is that it has not yet been possible to confer upon animals a genuine immunity against this infection.

The serumtherapy method may be employed even when the pathogenic agent has not been isolated. Under these conditions, use may be made according to the requirements of the case of one of the following procedures:

The serum from animals vaccinated by means of more or less modified virulent tissue. This is done, for instance, in regard to hydrophobia.

The blood obtained after the cure of the disease, whether the latter be spontaneous or inoculated. For diseases which are not transmissible to animals, man is experimented upon. After his recovery blood is taken from him which is employed for reinforcing the resistance of patients. This has been done notably in typhus fever, scarlatina, and rheumatism.

Lastly, in the case of a non-inoculable disease, fluids or extracts of tissues may be taken and injected into animals so as to arouse reactions on the part of the organism. This method, which is highly rational, has not yet received many applications.

It is likewise possible to employ extracts taken from organs in which the toxic substances accumulate or are produced. Drs. Hericourt and Richet have resorted to this procedure to prepare an anti-neoplastic serum.

These various procedures render the serum efficacious because they increase the resistance of the animal. This is demonstrated when the disease is inoculable, and this is assumed to be true when the disease is not inoculable.

This brief exposition suffices to show how numerous are the possible applications of serumtherapy. There is hardly a disease against which a serum cannot be prepared. Theoretically, the problems are easily solved while, as we shall see later, practical applications have not completely realized the hopes which were aroused by laboratory researches. The more we study the question the greater we find the difficulties to be overcome.

Various Organic Fluids Employed in Therapeutics. Therapeutic action being dependent upon soluble substances, serum as well as defibrinated blood may be used indifferently. As the latter product is more difficult of manipulation, the former is generally resorted to.

Delbet, however, has thought it advantageous to utilize the total blood just as it is obtained, when coagulation is prevented by means of an oxalate which precipitates the calcium salts. Nothing is easier than the preparation of serums. Two or three quarts (litres) of blood are taken from the jugular of a horse. The clot that forms is very solid, and the serum has a fine yellow amber color. It is kept in sterilized small vials, containing a few drops of some antiseptic oil or a little sublimated camphor. One of the inconveniences of the method is that successive blood-letting, especially when repeated at short intervals, often weakens the therapeutic action of the serum. This we have shown to be true at least as regards the antistreptococcic serum, and Marchoux has made the same observation. It has, therefore, been believed that it was possible to replace the blood by a fluid more easily procurable—milk, for example. The experiments of Brieger, Ehrlich, and Ketscher have established that this fluid possesses therapeutic properties, but it is ten times less active than serum, hence it cannot be used except when it is previously concentrated.

The curative fluid is generally introduced beneath the skin. Intravenous injection is employed only in laboratories. Introduction by the digestive canal does not seem highly reliable. Ehrlich demonstrated that the therapeutic substances present in the milk may impregnate the organisms of the young who ingest it, but this result is observed only in nursing animals. In fact, Ketscher has shown that the milk of goats immunized against cholera is curative when injected beneath the skin, but produces no effect when it is ingested. The active substance seems to be destroyed by the pepsin and pancreatic juice during digestion. When it is desired to introduce the serum by the alimentary canal it should, according to the advice of Dr. Chantemesse, be given in the form of enemata.

It is not necessary to dwell upon the rules of subcutaneous injections of serum. Except in certain special cases, the injection may be made into any part of the body. When, however, considerable quantities are to be introduced, it is advisable to operate upon the abdominal region. Here the fluid is better tolerated and most rapidly absorbed. The dose to be injected varies evidently according to the gravity of the case and the activity of the serum. The former factor can be appreciated by clinical observation alone; the latter may be determined with accuracy. Hence, from the very beginning of his researches, Behring endeavored to determine an exact measure for

the activity of serum. He first took as a unit the quantity of serum which insured against the smallest fatal dose of the toxin. He soon adopted, however, the method proposed by Ehrlich. This is practised in the following manner: The minimum fatal dose as regards the guinea-pig is determined, and then an amount of toxins equivalent to ten fatal doses is employed. This amount of toxin is called by Behring the *toxin unit.* This unit is then mixed with serum, and the whole is injected beneath the skin of guinea-pigs. Normal antitoxin is of such strength that 0.1 c.cm. neutralizes the toxin unit—*i. e.*, ten times the fatal dose. Behring called an *antitoxin unit* the amount of antitoxin contained in 1 c.cm., and, consequently, capable of neutralizing ten toxin units or one hundred times the fatal dose. When it is said that a serum has the value of ten units this means that 1 c.cm. neutralizes one hundred toxin units or one thousand fatal doses, or that the toxin unit is neutralized by 0.01 c.cm. A serum presenting one hundred units is of such potency that 1 c.cm. neutralizes one thousand toxin units or ten thousand fatal doses, and so on. This nomenclature is generally employed, except in the Pasteur Institute, where the preventive power and not the antitoxic action is determined. The animal which is to serve for the determination receives the serum, and the following day the minimum fatal dose is inoculated into it. The unit is the number of grams which 1 c.cm. of serum is capable of protecting. If, for example, a guinea-pig weighing 400 grams is preserved by 0.008 c.cm. of serum, 0.02 c.cm. would be required for 1000 grams. Therefore, 1 c.cm. would preserve 50,000 grams of the animal. Hence, it is said that the serum has the power of 50,000. Such is the unit of serum furnished by the Pasteur Institute. This method is not without advantage, but it presents a great inconvenience, for in employing the smallest fatal dose one may, perchance, experiment upon an animal endowed with a certain resistance, and attribute to the serum what is really due to the particular state of the animal. This source of error is avoided when the experiment is made with an amount of toxin ten times larger than the minimum fatal dose.

The method of mixture is applicable not only to toxi-infectious diseases, such as diphtheria and tetanus, but it may also be used to determine the action of a serum upon a living culture. It is well to note, however, that in the latter case the results are very different, according as a mixture of serum and microbes is injected or according as the serum and the culture are introduced at two different points

or successively at one and the same point. The curative action is far more marked when the serum and microbes come in contact.

Various Applications of Serumtherapy. The works to which the serumtherapy method has given rise are so numerous that it is impossible to present here a complete summary of them.[1] The diseases which may be treated by this method are divided into two groups according as the pathogenic agent is or is not known and cultivable.

The following is a list of infectious diseases for the treatment of which serumtherapy has been practised:

Anthrax.
Cholera.
Colon bacillosis.
Diphtheria.
Leprosy.
Glanders.
Bubonic plague.
Pneumococcosis.
Proteobacillosis.
Pyocyanobacillosis.
Hydrophobia.
Rheumatism.
Measles.
Scarlatina.
Staphylococcosis.
Streptococcosis.
Syphilis.
Tetanus.
Tuberculosis.
Typhoid fever.
Typhus fever.
Recurrent typhus.
Vaccinia and variola.

If we wish to make a complete study of serumtherapy we should add the diseases peculiar to animals, such as symptomatic anthrax, certain hemorrhagic septicemias, the disease of dogs, murr, and intoxications, notably poisonings by toxalbumins and venoms.

Cholera. Cholera has been the subject of important serumtherapic experiments, and the results obtained, besides their theoretic interest, seem to be of such a character as to lead us to hope that they will be applied to human therapeutics in the near future.

In 1892 Lazarus showed that a decigram of the serum of individuals cured of cholera is capable of protecting the guinea-pig against an intraperitoneal inoculation of cholera vibrios. This result, confirmed by various experimenters, was highly important. It was objected, however, that the serum of normal men and animals often possesses immunizing and curative properties. The result being uncertain, it was necessary to investigate what occurs as a result of vaccination. As early as 1890 Zasslein demonstrated that, under these conditions, the serum acquires very marked

[1] A complete description of serumtherapy and the principal bibliographical indications may be found in the report which the author presented to the Congres français de médecine: Des applications des serums sanguins au traitement des maladies. Nancy, August 6, 1896. Consult also: Landouzy, Les Sérotherapies. Paris, 1898.

germicidal properties, and, a few years later, Pawlowski and Buchstab, taking blood from vaccinated rabbits and guinea-pigs, succeeded in conferring immunity upon animals of the same species. These results were confirmed by Pfeiffer and Issaeff, and became the point of departure for a series of very important researches. Starting from the principle that the cholera toxin is contained in the vibrios and is not liberated until after the latter are disintegrated, Pfeiffer was led to immunize animals by injecting into them cultures sterilized by heat or chloroform vapor or by inoculating into them progressive doses of living vibrios. By these procedures he succeeded in obtaining a serum of extraordinary efficiency, but one which does not act except against vibrionic peritonitis. It fails when it is applied to animals inoculated by way of the intestine. The result which, from a theoretical standpoint, was of considerable importance, did not lead to any practical application. It was, therefore, necessary to take up the question under inspiration of the principles which had guided Behring. This was done by his disciple Ramson. In speaking of the mechanism of immunity, we have already referred (p. 564) to the result obtained by this author with an antitoxic serum quite different from the antibacterial serum obtained by Pfeiffer.

Metchnikoff, Roux and Taurelli-Salimbeni have prepared a very active antitoxic serum; 54 per cent. of the animals treated with this fluid survived, and 16 per cent. of the controls.

These highly interesting results thus open the field for therapeutic application. Of course, the phenomena are always more complex in man, in whom we must take cognizance of microbic associations which seem to play such a considerable rôle in the pathogenesis of cholera. It must also be demonstrated that the serum obtained by vaccinating an animal against one vibrio acts upon all varieties of the colon bacillus. Even leaving aside the vibrios, which seem to represent species or at least fixed races, like the bacillus of Finkler-Prior and the avicidal vibrio of Gamaleia, it is known that, in various cholera epidemics, quite different microbes have been found. Such, for instance, are the bacilli of Massouah, Ghinda, and Hambourg. On the other hand, Pfeiffer has shown that the serum of an animal immunized against one variety of microbe does not act upon the others. This fact is so constant that the author considers it a means of diagnosticating different bacilli. It is true that these results, which have not been completely confirmed by Sanarelli,

have been obtained in studying vibrional peritonitis and the serum which acts upon the figurate element. The toxin is probably always the same, and the antitoxic serum may succeed in all cases. This question is worthy of study.

Even before the recent researches on antitoxins, a few attempts were made upon man. During the epidemic of Hamburg, Freymouth investigated the effects produced by the serum of convalescents. Having learned that half a cubic centimetre injected into the peritoneum of a guinea-pig protects it against an inoculation of four-fifths of a cubic centimetre of virulent culture, he practised injections upon three patients. The first one who had been attacked for forty-eight hours received successively 10, 30, and 50 c.cm. a day. The patient at first seemed to feel better, but on the fifth day he grew worse, and death occurred on the sixth day. The second patient recovered after an injection of 30 c.cm. on the third day. On the sixth day, however, he still had vomiting and rhiziform diarrhea. The third case was that of a woman suffering from a slight attack. Her symptoms rapidly improved after an injection of 20 c.cm. These observations are too few in number to warrant a conclusion. At any rate, the method which consists in injecting the blood of convalescents cannot have a great future. Anticholeric serum must have an animal origin, and recent experiments with choleric antitoxins seem to have greatly advanced the question. The experimental study is nearly completed; clinical observation must decide the problem.

Colon Bacillus. As the colon bacillus constantly secretes toxic substances in the intestine, it is plain that a series of reactionary phenomena terminating in the production of antitoxins must occur within the organism. This is precisely what takes place. The serum of normal individuals may neutralize doses of *B. coli* ten times larger than those which are usually fatal. Thus we recognize a first spontaneous effort toward immunization. It suggested the next step, which consists in increasing the resistance of the organism by the usual procedures. Cesaris, Demel and Orlandi, Salvati and Gaetano demonstrated that the soluble products of the colon bacillus are capable of conferring immunity upon animals and imparting therapeutic characters to their sera.

Drs. Albarran and Mosny, having vaccinated animals by alternative injections of filtrates of the organs of animals dead from colon bacillosis and of living cultures, obtained a serum which, in

doses of 0.05 c.cm., immunized the guinea-pig against a virulent inoculation practised twenty-four hours later; 0.25 c.cm. sufficed to protect against an amount twenty times larger than the fatal dose. By studying the serum according to the method of mixture, it may be seen that one drop neutralizes the fatal dose. Finally, 2 c.cm. injected two hours after inoculation of an amount of culture equal to double the fatal dose saved the animals.

These results are sufficiently encouraging to warrant practical applications, notably in urinary infections, which Drs. Albarran and Mosny had particularly in view. It is more difficult to employ the serum under other circumstances, since it is not always possible to determine during the life of animals whether the symptoms are due to the colon bacillus or not. The serum cannot, therefore, be utilized except in certain surgical cases.

The close analogy existing between the colon bacillus and the bacillus of Eberth have led some experimenters to investigate whether the serum which antagonizes colon bacillary infection can likewise combat typhoid fever. Sanarelli demonstrated the mutual immunization by the two bacilli. C. Demel and Orlandi recognized that the serum of animals vaccinated against the colon bacillus prevents experimental typhoid infection. They have even made attempts on man and obtained improvement by treating typhoid cases with this serum.

In spite of their interest, these results should not be considered as proving that the anticolon bacillus serum is the specific of typhoid fever. Loeffler and Abel proved that, although the anticolon bacillus serum acts upon typhoid infection and the antityphoid serum acts upon colon bacillus infection, each of the sera is especially active when employed in the treatment of the disease against which the animal furnishing the serum has been previously protected. Here is a question of specificity which, while not absolute, is nevertheless undeniable.

Diphtheria. The employment of antidiphtheritic serum has completely transformed the prognosis of diphtheria. All statistics clearly establish that, under the influence of the new medication, the death-rate has diminished in extraordinary proportions and the period of convalescence considerably reduced. Moreover, the rapid evolution of the disease has enabled the physician to abandon tracheotomy and to substitute intubation for this operation. It would be right to devote the greatest part of this chapter to the

study of the antidiphtheritic serum. The question is so well known to-day, however, that we shall be contented with a summary of the most important facts.

Science is indebted to Behring for the two discoveries which led to the preparation of the serum. He demonstrated the certain means of immunizing animals against diphtheria, and he subsequently recognized that their sera became antitoxic. On this latter discovery antidiphtheritic serumtherapy is founded. In human therapeutics he employed the serum of sheep immunized by means of toxins attenuated by trichloride of iodine. Aronson used the serum of dogs. He later employed the serum of the horse. Roux and Martin also resorted to the horse. They added to the toxin one-tenth of its volume of Gram's fluid, which contains 1 gram of iodine, 3 grams of potassium iodide, and 100 grams of water. One-fourth of a cubic centimetre of the mixture is first injected, and the dose is progressively increased. It is thus possible at the end of three months of treatment to reach a dose of 250 c.cm. of the filtered culture.

The first therapeutic applications to the human subject were made in 1892 in the wards of Dr. Henoch, in Berlin. They were not very encouraging. Two years later, however, a new series of contributions appeared which determined conclusively the value of the serum. Ehrlich, Kossel, and Wassermann first reported the results of 233 inoculations practised upon children. The death-rate was 23 per cent. In a great number of cases the serum employed was not very active. Truly efficacious serum had been used only in 92 cases, and the death-rate had fallen to 12 per cent. About the same time Korte presented statistics of 121 cases. The death-rate was 33 per cent., while previous to the use of the serum it was 45 per cent. The figures of Aronson are far better. With his antitoxin he had a death-rate of 12 per cent. in a total of 255 diphtheritic children.

It would be superfluous to recall other less important statistics[1] published in Germany about the same period, indicating a notable decrease in the death-rate. The results obtained in France are by no means less favorable. In a very remarkable thesis Bayeux[2]

[1] For all statistics and bibliographical data relative to this first period, consult the article of Lépine: La sérotherapie de la diphtérie. Semaine médicale, 1894, p. 573. See also the report presented by Haushalter in the Congrès de Nancy, August, 1896.

[2] Bayeux. La diphtérie depuis Aretée le Cappodocien. Résultats statistiques de 230,000 cas. Thèse de Paris, 1899.

tabulated all the statistics and reached the conclusion that prior to serumtherapy the death-rate in diphtheria was 56 per cent. and had fallen to 16 per cent. after the introduction of this method.

It is at present generally agreed that a serum having 100 units is a very efficacious one, viz., that 1 c.cm. is sufficient to neutralize 100 toxic units, that is, 1000 fatal doses. Such is the strength of the serum furnished by the Institut Pasteur. The Belgian serum, prepared under the direction of Funck in the laboratory of Leopold Park, has a power of 200. In Germany the laboratory of Meister, Lucius, and Brüning, in Hoechst, furnishes three varieties of sera in vials of 10 c.cm. stamped by the government. Serum No. 1 has a power of 60 units per c.cm.; No. 2 is equivalent to 100 units, and No. 3 to 150. The contents of one vial, say 10 c.cm., is generally injected, and one of these three varieties is employed according to certain more or less clearly determined conditions. On the one hand, the dose is proportioned to the age and weight of the patient; on the other hand, serum No. 1 is made use of if the case is of moderate gravity and treated from the beginning. If the larynx is involved and if three or four days have already elapsed, then serum No. 2 is resorted to. No. 3 is used in cases of extreme gravity. In France, where one serum only is employed, the dose is diminished or increased according to the same indications as described with reference to the German method.

In order to appreciate the method it is necessary to take into account a number of factors depending upon the patient. In the first place, the age of the subject. In children diphtheria is always more serious than in adults, and it is the more dangerous the younger the child. From this point of view the latest German statistics are altogether convincing. The death-rate is still as high as $41\frac{1}{2}$ per cent. in children under one year of age. From one to two years of age it is 36.6 per cent. From two to five years it varies from 15 to 18 per cent. It is from 5 to 10 per cent. in children between five and fifteen years of age. It then falls to 2.7 per cent. from fifteen to twenty years of age, and to 0.8 per cent. from twenty to thirty years of age. The best results are observed at this last-named epoch of life. Beyond thirty years of age diphtheria is of rarer occurrence, but it is graver. The death-rate reaches 3.7 per cent. between thirty and forty years of age, and to 9.1 per cent. after fifty years of age.

Although the mortality remains high in children, it is among them that serumtherapy renders the most valuable service. In fact, adults recover quite often, no matter what the treatment employed; while children succumb because of their weak resistance to the toxin and on account of the extension of the process into the larynx. Hence, the death-rate is relatively less affected with reference to adults. It is reduced, especially in children, and notably in those suffering from croup. There is, however, an indispensable condition for success, that is, intervention as early as possible. On this point all clinical observers are in accord. In this connection the figures of the German statistics are highly suggestive. The death-rate is 5.4 per 100 when the treatment is begun on the first day, and 6.7 per cent. when it is instituted on the second day. It rises to 10 per cent. for the third day and to 23 per cent. for the fifth day. Prompt intervention has the double advantage of combating the disease while the intoxication is as yet unpronounced and secondary infections have not assumed a dangerous character, and by neutralizing the toxin early certain incidents of convalescence, such as paralysis are, perhaps, prevented.

In order to benefit the patient as promptly as possible by the effects of the serum, most bacteriologists advise an injection as soon as there is the slightest doubt as to the nature of a sore throat, or even as soon as any exudate whatever is present. At the same time a culture is prepared from the exudate, and, at the end of twelve to fifteen hours, the bacteriological diagnosis indicates the nature of the disease. The conduct of the physician is thus decidedly simplified. These principles, however, cannot be accepted without some reservation. Here we touch a delicate point which has already given rise to much controversy. For my part, I believe that physicians neglect too much the examination of the patients in the belief that they are able to establish a diagnosis, prognosis, and therapeutic indications by means of the data furnished by bacteriology. It seems to me that the diagnosis of diphtheria is not as difficult as it is said to be. In our isolation wards, where we receive all cases of anginas attended by the slightest whitish exudate, our pupils are accustomed to make the differential diagnosis. A diagnostic mistake occurred only in those cases of benign anginas which were cured almost without any treatment after cleansing of the throat. Two varieties of cases are observed in adults: The angina may present the indisputable characteristics of diphtheria. The serum

is then injected forthwith, and a culture prepared. In other cases the sore throat has the aspect of an herpetic angina. A culture must be made, and if on the following day Loeffler's bacillus is found, an injection may be made if necessary. Such has been our practise in our wards reserved for adults. In the case of children more prompt action is required. In fact, it is at that epoch of life that diphtheria is a grave disease. The course of the process must be arrested from the beginning and involvement of the larynx prevented. From this standpoint there is a radical difference between diphtheria of children and that of adults. In adults, diphtheria is a relatively benign malady which seldom kills of itself and which is particularly dangerous because of renal complications and consecutive paralysis. Such is not the case with children. Hence, as soon as there is the slightest doubt, serum injections must be resorted to. The few inconveniences of the serumtherapy method, the accidents which it may produce, and which will be referred to in the following chapter, are nothing in the presence of the urgency for prompt action. To wait for the result of the cultures would be to lose valuable time, the more valuable as it occasionally happens that no colony develops at the end of twelve or even twenty-four hours. In brief, in the case of a child presenting the clinical signs of diphtheritic angina, and especially of croup, serumtherapy must be applied immediately. In cases of pseudomembranous angina presenting the characters of herpetic sore throat clinically not resembling diphtheria, it is usually permissible to wait for the result of cultivation, and, when one has a certain amount of experience in diphtheria, bacteriological examination will confirm the data of observation. In order to comprehend the action of the serum we must study successively the modifications which occur in the local and general state of the patient. Locally, the serum causes exfoliation of the pseudomembrane. Very often the aspect is completely changed at the end of twenty-four hours. The exudates are softened, deliquescent, and the throat begins to be relieved of congestion. It is well to remember, however, that on the day following the injection an increase in the extent of the pseudomembrane may occur, for the reason that the parts were already invaded by the bacillus, and the exudate was produced in spite of the action of the serum. Coincidently, the engorgement of the lymphatic glands diminishes. Four or five days are generally required for the complete disappearance of the exudates. They sometimes

persist for a longer period, for a week or more; but they are then less extensive, occupying only a part of the tonsils, and the state of the patient causes no anxiety. While the local lesions subside, the general state improves. The patients experience a feeling of exhilaration, and they feel that the disease is checked. In consequence of the injection a profuse perspiration often occurs, which is a happy phenomenon, since it seems that sweating eliminates the toxin. The influence upon the temperature is variable. The serum frequently produces a transitory febrile movement, and if fever existed it falls at the end of twenty-four hours, while at the same time the frequency of the pulse diminishes.

If the case is one of laryngeal diphtheria the result is more remarkable by curtailing the duration of the evolution and favoring elimination of the pseudomembranes. Serumtherapy has left no longer any occasion for tracheotomy. The method of intubation has been resumed. This change in operative procedures has several advantages. Tracheotomy is not only dangerous, but by opening the trachea it permits the penetration of external germs or of microbes present in the wound, and thus favors the development of bronchopneumonia. Besides these immediate accidents, it may give rise to some remote ones. According to Landouzy, a great number of tracheotomized patients die at a later period in consequence of the development of pulmonary tuberculosis.

While there is universal agreement as to the facts above reported, doubt arises when we consider the rôle of the serum with respect to certain complications or grave manifestations, such as albuminuria. This question requires new investigation. At present it is impossible to form an opinion in view of all sorts of contradictory assertions. Some authorities contend that the serum prevents or diminishes diphtheritic albuminuria. Others, taking ground upon some experiments, assert that the serum gives rise to renal alterations. All that is possible to state is that albuminuria does not constitute a contraindication to serumtherapy. On the contrary, diphtheritic albuminuria, indicating a profound intoxication of the organism, demands active intervention. The serum cannot, of course, overcome pre-existing renal lesions. The important fact to observe is that serumtherapy does not aggravate it. Clinical facts are far too complex to permit a decisive opinion. The question should be taken up experimentally to determine whether antidiphtheritic serum gives rise to renal lesions or aggravates pre-existing alterations in animals.

As to paralyses, they are still quite frequent. It is hoped, however, that when serumtherapy is promptly applied while the toxins are not yet abundant and the nervous elements are more resistant, the accidents will diminish.

We have thus far endeavored to sum up the advantages of antidiphtheritic serum, disregarding the accidents which may be attributed to its use and which will be studied later on. We have shown what should be the line of conduct as regards the opportunity of injection. The question of concomitant treatment now remains to be considered.

It has been asserted that antiseptic lavage of the throat hinders the action of the serum, and many physicians at present oppose forcible removal of pseudomembranes. It seems to me that one should not have any preconceived ideas on these questions. It is better to be guided by observation of each patient. All that can be said is that in the treatment of diphtheritic anginas of adults we have obtained excellent results by means of lavage with boiled water, with solutions of carbolic acid and thymol, or cleansing with lemon juice. Finally, in certain cases we have noticed that concomitant injections of pilocarpine manifestly favor the action of the serum. The injections, which have been so fiercely opposed, seem to produce favorable results, provided the state of the heart and of the kidneys be carefully watched. When the heart is strong and the urine is not albuminous, the injection of one centigram of nitrate of pilocarpine rapidly ameliorates the general state and favors detachment of the pseudomembranes. In the case of adults it is a good auxiliary to serumtherapy, at least in certain instances.

Leprosy, Glanders. A few serumtherapy attempts were made by Carrasquilla against leprosy. The serum caused the return of sensibility, and the disappearance of the spots, edema and tubercles, and cicatrization of ulcerations, etc.

Few researches have been pursued on the serumtherapy of glanders. We have no others to cite except those of Chenot and Picq, who, out of ten inoculated animals, cured seven by injecting into them the serum of cattle, that is, a species naturally refractory to the disease.

Bubonic Plague. Yersin, Calmette, and Borrea succeeded in immunizing animals against bubonic plague by means of repeated inoculations of cultures heated for an hour at a temperature of 136.4° F. (58° C.). Dr. Roux has likewise immunized horses with

toxins. The serum thus obtained gave good results in inoculated monkeys (Wyssokowitz). In man it confers an immunity which lasts for about a fortnight. The therapeutic attempts made by Yersin in India reduced the death-rate from 80 to 49 per cent. In China, out of twenty-six sufferers treated in 1897, only two deaths occurred.

Pneumococcosis. The study of antipneumococcic serumtherapy has given rise to a great number of researches, of which Dr. Mosny speaks in a review.[1] As this author remarks, animals may be immunized by several procedures: One, accidentally discovered by A. Fraenkel, and systematically employed by some experimenters, consists in injecting dilutions of virulent microbes. It seems that, in order to succeed, it is necessary to employ cultures of moderate strength, for, according to Foa and Scabia, the highly virulent agents kill the animals or produce no effect at all—*i. e.*, do not immunize them. The attenuated cultures gave satisfactory results in the hands of Netter, Emmerich, Fowitzky, Foa, and Scabia.

Cultures sterilized by filtration or by the addition of a little chloroform are generally employed, but they must be heated to 140° to 149° F. (60° to 65° C.). Without this precaution the fluid is highly toxic and seldom immunizing. As in the case of diphtheria, the toxin may also be modified by means of the iodo-iodide reagent; an immunity persisting for three months is thus obtained (Foa and Carbone). Finally, for securing good results it is necessary to immunize by means of microbes possessing about the same virulence as those against which the animals are to be protected. It is likewise possible to immunize animals by means of filtered macerations of the organs of rabbits dead from pneumococcic septicemia (Mosny), by means of sterilized sputa or exudates, the blood serum or the serum produced by vesicatories (Klemperer). Whatever the mode of vaccination, the serum of animals that have been rendered refractory becomes immunizing and conservative.

Pneumococcic diseases being often benign in man, a serum of moderate activity may render great therapeutic services. It hastens recovery toward which the natural forces of the organism tend.

G. and F. Klemperer undertook the first practical applications. After injecting themselves with from 0.5 c.cg. to 3 c.cg. of serum of immunized rabbits, and thus proving the innocuity of the fluid, they

[1] Mosny. La vaccination et la guérison de l'infection pneumococcique expérimentale et de la pneumonie franche de l'homme. Arch. de méd. expér., 1893, p. 259.

injected from 6 c.cm. to 10 c.cm. into patients suffering from typhoid fever. The result was negative. They then operated upon six pneumonia patients, and with from 4 c.cm. to 6 c.cm. of serum obtained a fall in the temperature. In two cases the disease was immediately arrested. In another series of twelve cases G. Klemperer likewise observed very pronounced amelioration with doses varying from 5 c.cm. to 10 c.cm. Facts subsequently published by Foa and Carbone, Foa and Scabia, and Janson are no less encouraging. By tabulating the observations of these various authors the writer finds a total of thirty-nine cases. In only one case (an observation of Janson) the result was *nil*. In all the other cases there was very marked improvement. In twenty-one cases the crisis was produced on the following day or two days after intervention, and in several cases on the sixth, fifth, and even the fourth day. In view of such data it is difficult not to admit the favorable action of the serum.

Not only the serum of rabbits but also that of man may serve for therapeutic purposes. In some unpublished experiments, the results of which were indicated in a memoire of Prof. Bouchard, we recognized with Dr. Charrin that "the injection into rabbits of blood serum obtained by venesection from a man suffering from pneumonia in the stage of defervescence or seven days after, renders these animals refractory to inoculation with pneumococcus, and this four days and even eleven days after the injection of the serum."[1] Andeoud[2] applied these experimental results to man. He injected into two patients the serum drawn from a pneumonia convalescent. In one of the cases two injections sufficed to bring about a crisis on the sixth day. In the other instance the disease terminated on the fifth day, fifteen hours after the first injection. In a communication addressed to the Congress of Rome, Maragliano announced that he had obtained thirty-nine favorable results by the employment of the serum of immunized animals or of cured patients. In attempts of this kind, however, the serum of the dog should never be resorted to. This serum, far from preventing the infection of the rabbit, favors it. An observation of Foa and Scabia proves that it acts in the same manner upon man. An injection of 2 c.cm. or 3 c.cm. of the serum of a dog which had previously received virulent cultures

[1] Bouchard. Sur les prétendues vaccinations par le sang. Revue de médecine, January, 1892, p. 15.

[2] Andeoud. Serothérapie dans la pneumonie. Revue méd. de la Suisse romande, February, 1893.

of pneumococci, caused a notable aggravation of the general phenomena, an increase in the fever, and a manifest delay in recovery.

Although pneumonia is a disease which, in the majority of cases, naturally terminates in recovery, there are other pneumococcic manifestations which almost invariably cause death. Meningitis is among the number. Here is a subject for investigation which is of great importance and necessary for a final judgment of the value of serums. In fact, there is already a recorded observation which, although unique, is none the less encouraging. Righi[1] observed a seven-year-old child presenting the typical symptoms of acute meningitis. Examination of the blood revealed the presence of the pneumococcus. On the fifth day the author injected 1 c.cm. of serum taken from a convalescent of pneumococcic meningitis. The symptoms improved and the patient recovered on the eighth day. The serum injected was endowed with energetic germicidal properties and proved to be preservative and curative for mice and rabbits.

Proteobacillosis. It has long been known that it is possible to immunize against the *proteus* with soluble substances or even well-defined products like neuridin. De Nittis[2] has made known a mode of immunization by means of living cultures and succeeded in obtaining an active serum. He showed that the guinea-pig could endure an intraperitoneal injection of from 3 c.cm. to 3.5 c.cm. of a culture 1.5 c.cm. to 2 c.cm. of which, when introduced by the veins, killed rabbits weighing 2 kilograms within twenty-four hours. The serum of guinea-pigs thus treated proved to be very efficacious. A dose of 2 c.cm. per kilogram of animal suffices to protect rabbits against inoculations which kill the controls in twenty-four hours.

Pyocyanobacillosis. Pyocyanobacillosis or pyocyanic disease has been the subject of important serumtherapic investigations. The experiments pursued by Bouchard[3] led this scientist to formulate certain conclusions, several of which were then absolutely new, and which, from the standpoint of general pathology, are of such importance that it will be interesting to give a résumé of them here.

After determining that the blood of naturally immune animals has but a slight therapeutic action, and that, in order to obtain an efficient serum, it is necessary to employ the blood of immunized animals,

[1] Righi. La sieroterapia nella meningite. La riforma medica, 1894, iii. p. 566.

[2] De Nittis. Sérothérapie du Proteus vulgaris. Société de biologie, June 13, 1896.

[3] Bouchard. Les prétendues vaccinations par le sang. Revue de médecine, January, 1892.

Bouchard demonstrated that the serum is as active as, and even more energetic than, defibrinated blood. In order to prove that the effects were due to the serum, viz., to soluble matters and not to morphological elements, this author filtered the fluids through porcelain. The results were not modified. He then studied the urine of animals which had received blood of immunized animals and found that it did not confer immunity. It did not act otherwise than the urine of animals into which sterilized cultures had been injected. Moreover, he showed that the immunity conferred by the serum is of short duration. If it existed on the eighteenth day it disappeared on the twenty-second. The serum exerts an immediate protective action which gradually diminishes, while the bacterial substances at first weaken the resistance and subsequently increase it. Hence it may be concluded that the active substance of the serum is rapidly destroyed within the organism of the animal into which the injection has been made, and that the immunity produced by the serum is due not to a reaction of the organism, but simply to the introduction of some germicidal substance. Finally, a last distinction must be established between the immunizing substances of cultures and those of the serum. The former resists a temperature of 239° F. (115° C.), the latter are destroyed between 140° F. and 149° F. (60° C. and 65° C.), and at the same time the germicidal action disappears.

Staphylococcosis. The first experimental attempt of serumtherapy was directed against the staphylococcus. Héricourt and Richet, in a study on the *staphylococcus pyosepticus*, which is a variety of the *staphylococcus albus*, recognized that infection in a rabbit could be prevented by injecting the blood of dogs. The result was especially manifest when use was made of dogs that had recovered from a previous inoculation of staphylococci.

The method, which consists in employing the serum of animals cured from a virulent inoculation, is too uncertain for generalization. It was, therefore, necessary to immunize by the usual procedures, notably with sterilized cultures. Drs. Rodet and Courmont discovered the interesting fact that the soluble products of staphylococci, far from increasing the resistance, diminished it and predisposed the organism to infection. By continuing their researches, however, they succeeded, by means of alcohol, in extracting a substance capable of conferring upon animals a sufficiently marked immunity. Dr. Courmont subsequently learned that the serum of animals thus prepared has no germicidal power, but possesses the property of attenuating

microbes and causing them to lose their virulence. The practical importance of this result is evident.

It is not only by employing substances soluble in alcohol that animals may be immunized. Viquerat arrived at the same result by a procedure first employed by Behring. Viquerat injected a 1:2000 solution of trichloride of iodine into the neighborhood or the interior of a staphylococcic abscess. Under the influence of this treatment the abscess was rapidly cured, and its contents were transformed into a serum which was filtered in order to free it from microbes which it might contain. This fluid, like the blood serum of cured individuals, possesses preventive properties against the intravenous inoculation of staphylococci in rabbits. Having thus obtained a serum of a preventive power of $\frac{1}{12500}$, the author injected from 10 c.cm. to 65 c.cm. of it into various patients, and obtained a speedy cure of furuncles, paronychia, and even osteomyelitis. He next immunized animals by means of cultures to which trichloride of iodine was added, and obtained from goats a serum endowed with a power of from 10,000 to 500,000. When injected into patients this serum caused a very intense reaction at the point of the lesion. At the end of fifteen or twenty hours the phenomena improved and notable amelioration resulted. Finally, Kose immunized a goat by first injecting it with cultures attenuated by heat, then more and more virulent fluids. The serum of this animal, although devoid of all germicidal action, increased the resistance of inoculated rabbits, but did not save them; they died less rapidly, however, than the controls. It is true that the goat was insufficiently immunized.

Streptococcosis. The history of antistreptococcic serumtherapy has been presented in such a faulty way, except in Bonnet's[1] work, that we think it worth while to re-establish the succession of investigations by indicating the dates.

In order to prepare an efficient serum it is always necessary to reinforce the immunity of the animals. Several procedures were used with quite variable results. We may group the attempts in the following manner:

1. *Immunization by Living Cultures.* Lingelsheim,[2] who employed all cultures heated to 145.4° F. (63° C.) for an hour, obtained only

[1] Bonnet. La sérumthérapie dans les affections streptococciques. Gazette hebdomadaire, 1895, p. 229.

[2] Lingelsheim. Exp. Untersuchungen über morpholog, cultur, und patholog. Eigenschaften verschiedener Streptokokken. Zeitschr. f. Hygiene, Bd. x., Heft 2, 1891.

negative results. With cultures attenuated according to Behring's procedure, viz., by means of trichloride of iodine, he succeeded in immunizing only two mice out of twelve. By operating upon rabbits, De Paolis[1] rendered the animals refractory by injecting into their veins non-virulent cultures. We succeeded in conferring immunity upon animals by making successive inoculations of virulent cultures beneath the skin of their ears. The reactions were less and less intense and finally became so mild as to give rise only to circumscribed abscesses.[2]

2. *Immunization by Sterilized Cultures.* As in other infections, immunity from streptococcic infection may be conferred by means of soluble products. A little difficulty is encountered here. Sterilized cultures contain two groups of substances with antagonistic action. Some of them diminish resistance. Others increase it. If from 5 c.cm. to 12 c.cm. of a culture filtered through porcelain be injected into animals, subsequent inoculation of the living microbe produces death far more rapidly than when no previous intervention had taken place

In one case we saw an animal thus succumb eleven times more rapidly than the control. It is to be noted that no relationship exists between the quantity of the toxic substance injected and the degree of predisposition created by its injection. If, however, cultures sterilized by heat are employed, the effects are quite different. Rabbits which received from 5 c.cm. to 30 c.cm. of the fluid thus obtained, and which were inoculated from four to thirty days later, survived while the controls died within a few days.[3]

We must remark, however, that these results are perhaps applicable only to rabbits or at least to certain animal species. There are others in which injections of filtered cultures seem to increase the resistance. Such is the case with the horse. On the other hand, the employment of cultures sterilized by heat is not without danger. Very virulent cultures, or even cultures of moderate activity in which certain varieties of streptococci are developed, contain noxious substances which cannot be destroyed by heat. Under these conditions their injection gives rise to emaciation, at times cachexia and death,

[1] De Paolis. Sulla proprieta vaccinale dello streptococco dell' erisipela. La riforma medica, 1889, No. 200.

[2] Roger. Modifications du sérum à la suite de l'érysipèle. Société de biologie, October 25, 1890.

[3] Roger. Action des produits solubles du streptocoque de l'érysipèle. Société de biologie, July 4, 1891.

and may fail to confer immunity. These remarks account for a great many contradictory facts.

3. *Immunization by Mixed Procedures.* Mironoff[1] obtained good results by combining the proceedings hitherto described. He employed successively, in the same animal, attenuated cultures and virulent cultures in progressively increasing doses. He thus succeeded in rendering animals able to bear, without reaction, quantities of virulent cultures ten times larger than those which are fatal for the non-immunized.

Whatever the method employed for immunizing animals, the serum of the vaccinated acquires therapeutic properties. This was proved by the author's experiments[2] and by those of Mironoff.[3] According to this author the action of the serum is proportionate to the dose employed; but it does not affect the local lesions. As the result of extremely remarkable researches, Marmorek[4] succeeded in preparing a serum by means of cultures of incredible virulence. To kill a rabbit a dose of 0.000,000,000,01 c.cm. of the culture is sufficient. The rabbits into which the serum is injected a few hours before the inoculation resist this microbe. Those that are first inoculated and then treated a few hours later also survive. Finally, Parascandolo immunized animals against the staphylococcus and streptococcus. He employed highly virulent microbes which he cultivated in bouillon containing sugar. The cultures sterilized by the addition of 5 per cent. of phenol were injected into dogs, rabbits, and guinea-pigs in progressively increasing doses. The serum of animals thus prepared neutralizes *in vitro* the toxins and the microbes; its action proved preventive and curative in animals into which these pyogenic microbes were inoculated and had caused either a generalized infectious process, such as puerperal fever or septicemias, or a localized process like erysipelas.

What renders these investigations interesting is the fact that this author succeeded in cultivating several pyogenic microbes in the same medium, and thus obtained a serum which was efficacious against species that are often found associated.

[1] Mironoff. Immunisation des lapins contre le streptocoque. Arch. de médecine expér., 1893, p. 441.

[2] Roger. Contribution à l'étude expérimentale du streptocoque de l'érysipèle. Revue de médecine, 1892, p. 953.

[3] Mironoff. Loc. cit., 1893.

[4] Marmorek. Sur le streptocoque. Société de biologie, February 23, 1895. Streptocoque et sérum antistreptococcique. Annales de l'Institut Pasteur, July, 1895, p. 593.

Thus a number of experimenters arrived independently at identical conclusions, viz., possibility of vaccinating animals against the streptococcus; possibility of preparing a serum efficacious against experimental streptococcic infections.

Hence, it was natural to attempt the treatment by antistreptococcic serum in human diseases. The first endeavor was made by Gramakowsky, who treated two cases of erysipelas. The result was not very encouraging, since one of the patients died. On February 23, 1895, we reported to the Biological Society two successes obtained in the wards of Dr. Charrin.[1] They were two women suffering from puerperal fever, one of them profoundly infected. Both survived. The following month we reported two other cases, and on the same day Dr. Marmorek[2] announced that he had successfully treated forty-six patients suffering from erysipelas. From this moment on contributions succeeded each other in France as well as in other countries. The results were quite variable and gave rise to a good deal of discussion.

In order to practise serumtherapy on man it has been necessary to resort to animals capable of furnishing great amounts of blood. Hence, the horse was chosen.

Following the suggestions drawn from our investigations upon rodents, we immunized animals by means of streptococcic cultures sterilized by heat. It is likewise possible to confer immunity by means of toxins obtained by filtration of the cultures through porcelain. Dr. Vinay resorted to the latter procedure. Finally, Marmorek injected into the veins progressively increasing doses of living cultures of his highly virulent streptococcus.

All these methods are evidently good. Drs. Denys, Leclef, and Marchand, who took up the question and prepared serums by means of living cultures or of toxins, obtained very encouraging results in both cases. The only point that now requires investigation is whether the serums are more efficacious when they are prepared by one or the other of these various procedures and whether all are equally harmless. The serum obtained by means of living cultures has at times caused abscesses and erysipelas patches at the point of injection. This result is due to the persistence of the streptococci. This inconvenience is not, however, of a nature to

[1] Charrin et Roger. Essai d'application de la sérumthérapie au traitement de la fièvre puerpérale. Société de biologie, February 23, 1895, p. 124.

[2] Marmorek. Le sérum antistreptococcique. Ibid., March 30, 1895, p. 230.

cause abandonment of the method, but it is well to be aware of the fact and take some precautions—to wait longer before bleeding the animals or to filter the serum through porcelain.

In order to prove the action of the serum it was thought that cases of erysipelas should be experimented upon. Hence, Dr. Chantemesse employed the serum of Marmorek in 501 cases, and the death-rate was 2.59 per cent. A close examination of these facts permits a division of them into three groups: The first includes those cases in which the serum employed had a strength of 1 per 7000, with a death-rate of 1.68 per cent. The second comprises those cases in which the serum had a strength of 1 per 2000, with a mortality reaching 6.54 per cent., that is, a far greater percentage than by usual treatment. Finally, by a new serum having a strength of 1:30,000 the death-rate fell to 1.03 per cent.

Some objections were raised against these results. Dr. Bolognesi remarked that just as favorable results may be obtained by the simplest treatment. In the wards of Juhel-Renoy the death-rate did not exceed 3.5 per cent., and occasionally, it fell to 1.21 and even to 0.9 per cent. As a matter of fact, it is evident that an adult of good constitution does not generally die from erysipelas. The aged persons who succumb had, for the most part, some organic lesion, particularly of the liver.

The serum should, therefore, be reserved for grave cases in which it may render service, for cases characterized by relapses and in prolonged forms, as well as for erysipelas of the newborn, although in this last instance it does not seem to be very efficient.

The action of the serum in cases of surgical and puerperal septicemias deserves particular study. Puerperal fever is of far more frequent occurrence than is generally believed. From 1884 to 1893 the statistics of the city of Paris registered 3000 deaths due to this cause. This is under the real figures, as a good many cases go under different designations. The results obtained with the serumtherapy treatment have been quite variable. This could be well foreseen, since intervention takes place too tardily in most cases, or the case is one of mixed infection, or perhaps, insufficient doses of the serum are employed. After the publication of our results very encouraging observations were reported by Drs. Josué and Hermary, Jacquot, Marmorek, Chrobak, Vinoy, Denys, and Leclef.[1] On the other hand,

[1] Denys and Leclef. Sur le sérum antistreptococcique (report by Rommelaere). Acad. de Méd. de Belgique, December 28, 1895.

in the Obstetrical Society of France (April, 1896), the majority of obstetricians related rather disappointing observations. Charpentier had had a death-rate of 35 per cent., Bar and Tissier 50 per cent. In the cases which we treated the results were far better. Our statistics, which have the defect of being too small, containing only twelve cases of puerperal fever, may be divided into two groups: Those in which the treatment was insufficient—*i. e.*, in which too small amounts of serum were injected. Such were two cases, one of whom died. In the other ten cases the treatment, which was at times tardily instituted, yielded nine recoveries and only one death. Several of these patients would have recovered without the serum. Several others, however, presented symptoms of extreme gravity; one, among others whom Prof. Pinard was called to see, was pronounced to be in a hopeless state. In order to obtain therapeutic effects, considerable doses of the serum must be employed: the introduction of 60 c.cm. per day—30 in the morning and 30 in the evening. In one case we injected without any inconvenience 300 c.cm. in four days. The patient, who was comatose at the moment of intervention, recovered and was seen by us ten months later. She presented no disturbance in consequence of this active treatment. The effects of the serum are observed in the local lesions as well as in the general condition of the patient. Locally, the vulval wound modifies, the congestion disappears, and the wound assumes a good aspect. In one case the pseudomembranes which covered the vulva and vagina, and were quite intimately adherent to the mucous membrane, were easily detached, exactly as when antidiphtheritic serum is injected in cases of anginas. At the same time the general state is improved, the patients experience a feeling of exhilaration, and the skin becomes moist. The modifications in the temperature are quite variable. In some instances fever was not influenced. In other cases it fell gradually or abruptly. In all the successful cases, convalescence, which is usually so long after puerperal fever, was remarkably shortened.

We may conclude from our personal observations that antistreptococcic serum is a useful auxiliary in the treatment of puerperal fever. We believe, however, that it should not be employed to the exclusion of all other therapeutic measures; and we do not accept this mode of action with reference to diphtheria in which it is far more justifiable. We think that all measures of treatment should be utilized, and, according to the cases and the indications of each, curettage

may be employed, which may remove placental fragments often filled with microbes of all descriptions, as well as intra-uterine irrigations, gastrointestinal antisepsis, and, above all, cold baths. Observations taken under these conditions would necessarily be less clearly demonstrated and more complex; but what we must look for is not the demonstration of the efficacy of a method at the risk of the patients' lives. It would not be right to make such experiments. Our duty is to benefit those under our care by all therapeutic means at our disposal. In order to obtain results from the serum we must not wait until the last moment. On the contrary, we should intervene from the very beginning of manifestations, and inject large doses, and combine serumtherapy with the other methods of treatment. Such is, in our opinion, the line of conduct to be followed in the presence of puerperal fever, or rather of a puerperal woman suffering from fever. It is hardly necessary to say that even under these conditions we cannot save every patient, and this for several reasons: puerperal fever is not always due to the streptococcus. It often depends upon bacterial association. Besides the streptococcus, there may be found the staphylococcus, the pneumococcus, the pneumobacillus, the colon bacillus, the septic vibrio, etc. Nevertheless, the serum seems to be efficacious against at least one of these microbes; that is, the pneumobacillus. We have observed three instances of this kind.

One of them concerned a woman who had an attack of very grave puerperal fever. The symptoms rapidly yielded after two injections of the serum, 30 c.cm. each. Examination of the lochia did not reveal any other microbes than the pneumobacillus. The second case was that of a puerperal woman, in the lochia of whom both streptococcus and pneumobacillus were found. One injection sufficed to overcome all the disquieting symptoms. The last instance concerned a woman suffering from a suppurative salpingitis, upon whom laparotomy was practised and the tubes were extirpated. During the operation the tubal abscess burst and the pus spread into the peritoneum. Septicemic phenomena developed, and on the following day, the patient being in a very serious condition, antistreptococcic serum was injected into her. In four days the manifestations subsided. Examination of the pus revealed the presence of the pneumobacillus alone.

The cultures obtained from this last case were highly virulent. One cubic centimetre when injected into the veins caused death

in rabbits within twenty-four or thirty-six hours. Four or five cubic centimetres of antistreptococcic serum, injected at the same time that the inoculation was made, sufficed to save the animals. The dose may seem too high. This experimental result, however, is entirely in harmony with clinical observations. Still, it is not to be concluded that antistreptococcic serum is efficacious against the pneumobacillus. It was such against these samples, and even in the three cases it acted far more rapidly and energetically than when we employed it in infections due to the streptococcus.

Our last observation leads us to say a word regarding the employment of the serum in surgical septicemias. The rules are the same as in puerperal fever. The results which we obtained were very satisfactory. The serum was tried in three cases, and all recovered. Marmorek also obtained successful results under the same conditions.

The serum has not yet been used in cases of diffuse phlegmons or streptococcic suppuration. It is not likely that it would prove efficacious. Likewise, we know very little as to its rôle in cases of bronchopneumonia. A few attempts were made in scarlatina by Marmorek, Josias, and Baginsky. The results were quite uncertain, which is not to be wondered at, since it is not known what rôle is played by the streptococcus in scarlatinal manifestations, even in the anginas.

We have expounded at some length upon antistreptococcic serum-therapy, because a future seems to be reserved for this method. No doubt the results are not yet perfect. They will be better when more active serums are obtained, and particularly when the treatment is instituted from the very start of the morbid manifestations. It is evident that success is not to be expected in every case, since the infections are sometimes mixed, and the serum cannot be efficacious against all the streptococci. An animal which is immunized against one variety, furnishes a serum that is powerless against the other varieties. It is well, therefore, to immunize animals by injecting cultures obtained from various sources. Such is the method at present employed by Denys. Lastly, as regards puerperal infection, we must take into consideration the rôle of the living microbes and that of the bacterial toxins. Numerous examples, notably the study of cholera cases, show that, according to the procedures of immunization, the animals furnish either germicidal or antitoxic serums, that is to say, sera acting upon the living microbes or upon their secretions. Hence, it is necessary to prepare serums endowed with both

of these properties, so that the antitoxin may combat the action of harmful products already diffused in the organism, while the antibacterial substance hinders the further development of the figurate elements.

Tetanus. Antitetanic serum is also the work of Behring and Kitasato. These authors discovered the means of immunizing against the microbe. They succeeded with toxins treated with trichloride of iodine or cultures prepared in thymus gland bouillon. Immunity was subsequently obtained by other procedures as well. Vaillard employed filtered cultures which were attenuated by heat between 122° and 140° F. (50° and 60° C.). Roux and Vaillard employed, as in diphtheria, a mixture with iodized water.

The serum of vaccinated animals was first studied by Behring and Kitasato, who recognized that it possessed the same property as the antidiphtheritic serum. It neutralizes poisons—*i. e.*, it is antitoxin. This result immediately led to therapeutic investigations, since, as is known, tetanus is one of the infectious diseases in which intoxication plays the principal rôle. The results obtained by Behring and Kitasato at first appeared very encouraging. These authors declared that antitetanic serum protects the animal into which it is injected against tetanus, and may even cure the established disease. They asserted that it was possible to save a mouse already presenting the characteristic contractures.

These experiments, however, were controlled by Tizzoni and Cattani, Vaillard, and then by Kitasato himself, but gave negative results from a therapeutic standpoint. Roux and Vaillard subsequently proved that the serum, when injected before inoculation, protects the animals. When it is introduced coincidently with the toxin or a little later, it attenuates the manifestations and permits only a local tetanus. But it is absolutely inefficient when injected into animals already presenting contractures.

This last result raises a theoretical question of considerable interest. The inefficiency of the serum is not well understood if it is admitted that the antitoxin neutralizes the toxin. On the other hand, if it is supposed—and this is the prevailing theory—that antitoxins act by increasing the resistance of the anatomical elements, perhaps by preventing their impregnation, it is then conceivable that injection of the serum will not suffice to arrest the evolution of the disease. Sahli, whose theory is similar to that advanced by Courmont and Doyon (p. 413), goes further. He

believes that the toxins are often eliminated when the manifestations appear, but that they leave in the nervous system alterations which follow an independent course. The serum does not act upon these lesions any more than the salicylate does upon rheumatic endocarditis.

The serum is employed rather as a preventive. It is employed for man when a wound is contaminated by soil, particularly in countries where tetanus is frequent or in individuals who come in contact with horses. In veterinary medicine it renders numerous services. It is often injected as a prophylactic into horses which are about to be castrated.

The serum is still administered to man in subcutaneous injections, and in large doses in cases of established tetanus. Successes are recorded from time to time. Several such observations, however, are liable to criticism. It has, therefore, been thought that the mode of introduction of the serum required some modification. As a result of their investigations on cerebral tetanus, Roux and Borrel conceived the idea of injecting the serum directly into the cerebral substance of tetanic patients. Experiments pursued upon animals seemed to demonstrate the value of the method.

The first application to man was made by Chauffard and Quénu. The patient recovered. Two months later, Garnier published the report of a successful case observed in our wards. It was a case characterized by a slow course. During the first three days the tetanus was benign. The fourth day, the state being aggravated, we decided to intervene. Six cubic centimetres of concentrated serum, equivalent to 15 c.cm. of the ordinary serum, were injected into the two cerebral hemispheres. Simultaneously 116 c.cm. were injected beneath the skin. At the end of three days amelioration was manifest. Recovery was complete a month later. Convalescence was disturbed by psychic disorders and erotic delirium. These phenomena were transitory. By collecting the published observations, a death-rate of 75 per cent. was found; that is larger than the average death-rate, which does not exceed 70 per cent. As nothing regarding this method has been published for some time, it may be supposed that it has been almost abandoned. Is it at least inoffensive? The majority of authors suppose it to be so. In the case of Garnier, however, psychic disorders, though of a transitory character, developed in consequence of the injection. In another case observed by us and published by Dr. Robert, death

occurred twenty-four hours after the injection. The necropsy revealed acute edema of the meninges and, in one of the cerebral lobes, a cavity filled with a sanguinolent fluid. It may well be asked whether such a lesion in so delicate an organ may be considered indifferent.

Instead of introducing the serum into the brain, Sicard injected it into the lumbar subarachnoidal cavity. The results obtained in dogs were very encouraging. In man the method does not seem to have been successful. Thus we find, with reference to tetanus, the antagonism which we noted on several occasions between the results obtained in laboratories and facts of clinical observation. This does not mean that the importance of experimental investigations is any less valuable; but it should be recognized that human pathology is extremely complex, and, therefore, it is necessary to pursue new researches and make new attempts.

Tuberculosis. Richet and Héricourt[1] were the first to attempt antitubercular serumtherapy by injecting the blood of dogs into the peritoneum of rabbits inoculated with cultures of avian or bovine tuberculosis. The quantity of blood transfused varied from 16 to 41 grams. The mortality of the controls was 55 per cent., and that of the transfused 17 per cent. Soon after, Bertin and Picq made analogous attempts with the blood of goats, which are reputed to be immune to tuberculosis. By employing 2.5 grams per kilogram of animal they succeeded in preventing or arresting the development of the disease.

These results were soon applied clinically, and a few successes seem to have been obtained by subcutaneous injections of the blood of dogs and goats. In spite of these encouraging results, the employment of the blood of normal animals did not lead to a definitive method. The serum of naturally immune animals almost never possesses true curative power, for the reason that natural immunity is always contingent and is never absolute. In regard to tuberculosis, this law is the more accurate, as we know of no mammalian that is endowed with a notable resistance. The serum of the gallinæ, the only animals enjoying a certain immunity, does not possess the power of arresting the evolution of tuberculosis in mammalia into which it is injected. Extracts of the organs have not proved to be any more efficacious.

[1] Héricourt and Richet. Influence de la transfusion péritonéale du sang de chien sur l'évolution de la tuberculose chez le lapin. Société de biologie, March 2, 1889.

Experimenters were, therefore, led to investigate whether it was possible, by various procedures, to confer artificial therapeutic power upon the serum of certain animals. A good many attempts were made in this direction. In spite of their apparent multiplicity, the procedures employed are divisible into three groups: 1. Employment of living cultures. 2. Employment of sterilized cultures. 3. Mixed method, in which both soluble products and living cultures are made use of.

1. *The Serum of Animals Treated with Living Cultures.* This procedure was variously utilized. Héricourt and Richet, having obtained a relative immunity in dogs which had received avian tuberculosis, were naturally led to study the therapeutic action of their fluids. They employed the serum obtained by inoculating avian tuberculosis beneath the skin of the dog. This fluid, which the authors called *phymoserum*, when freed from leucocytes, is found to possess well-marked immunizing properties with regard to rabbits. The authors, however, seem to have abandoned this method in order to prepare a *neoserum* with animals inoculated with human tuberculosis.

The procedure of Héricourt and Richet consists in inoculating with human tuberculosis animals of slight susceptibility, such as asses and dogs. In a first series of experiments the serum was furnished by an ass which received, one month previously, an injection of virulent human tuberculosis. While the control guinea-pigs died at the end of two months, out of four guinea-pigs treated, two were still living at the end of seventy-one days. In another note the authors announced that they had inoculated dogs with tubercle bacilli previously freed from tuberculin by washing. The inoculations were made into the veins, and the animals were bled at the end of ten days. The serum was used to treat a woman, thirty-four years of age, in whom a very manifest amelioration was observed. A few months later Redon and Chenot announced that it was possible to prevent tuberculosis in rabbits and guinea-pigs by injecting into them the serum of asses or mules which had previously been inoculated with tuberculosis and presented no lesion in consequence of this operation. The results were still better when the serum of horses first treated with tannin was used than when active tubercular virus was employed.

Evidently here are very interesting results which are, nevertheless, open to criticism. The dog, the ass, the mule, and the horse are far

from presenting a natural resistance as pronounced as was once believed. In those cases in which dogs and goats withstood virulent inoculations and in those instances in which animals of this same species presented only very discrete lesions, Silvestrini obtained no notable effect by treating tubercular guinea-pigs with their sera. With Cadiot we tried, with no greater success, the serum of an ass which presented a voluminous local lesion produced by inoculation of human tuberculosis. The guinea-pigs which received the serum died more rapidly than the controls. On the other hand, Broca and Charrin obtained encouraging results in man. The serum employed was that of dogs suffering from a local tubercular lesion. The injections, when made into patients affected with lupus or fungous ulcerations consecutive to incomplete surgical intervention, produced notable amelioration in the lesions.

How are these favorable results to be explained? Can it be assumed that the serum acted simply like the normal serum of the dog, which also possesses the power of improving cutaneous tuberculosis (Feulard)? This interpretation is inadmissible. It is well, however, to take into account the possibility of an action comparable to that of tuberculin. In fact, it seems that in the course of tuberculosis the blood contains a substance analogous to that extracted by Koch from cultures of his bacillus. The blood of tubercular dogs possibly represents a dilution of tuberculin which is too weak to give rise to dangerous reactions, but sufficient to ameliorate local lesions. This explanation seems to me the more admissible, since Koch's lymph is most efficient in lupus and external tuberculosis.

While virulent cultures do not seem to yield good results, it may be hoped that attenuated cultures will prove more satisfactory. Researches published by Schweinitz and Dorset tend to prove this. Two horses received considerable quantities of attenuated cultures —as much as 4590 c.cm. in eight months. The serum of the animals thus treated possessed the power of prolonging the life of tubercular guinea-pigs and even of saving some of them.

2. *Serum of Animals Treated with Sterilized Cultures, Extracts, Tuberculin, etc.* In view of the principle that the presence of a poison causes the elaboration of an antitoxin in the organism, it was natural to investigate what would happen in animals as a result of injection of tubercular poison, notably tuberculin. Héricourt and Richet experimented with the serum and milk of female asses which had previously been injected with Koch's lymph. The animals treated

with these products succumbed more rapidly than the controls. A few months later, Dr. Boinet announced that the serum of tuberculinized goats protected guinea-pigs into which an inoculation of virulent tuberculosis was afterward made. When employed in patients the serum produced amelioration in mild forms of tuberculoses, but it was ineffective in individuals with cavities and in those presenting febrile movements or hemoptysis.

The presence of an antituberculin in the blood of animals treated with tuberculin was proved especially by the investigations of Behring and of Niemann. Behring, in collaboration with Wernicke and Knorr, found antituberculin in the blood of man and animals which had been injected with progressively increasing amounts of tuberculin. In order to demonstrate this these authors injected fatal doses of tuberculin into tubercular guinea-pigs. Those animals which received the serum at the same time the tuberculin was injected did not die. Niemann published analogous experiments. He resorted to very different animals—dogs, goats, guinea-pigs, white rats, porcupines—and injected into them progressively increased doses of tuberculin, or, still better, a precipitate obtained by means of alcohol, so as to free it from glycerin. He thus conferred upon them a certain immunity against virulent inoculations. He then tried the serum upon tubercular guinea-pigs, with the following results: 40 cg. of tuberculin killed the animals in a period of time varying from fourteen to seventeen hours. The same dose, when mixed with 8 c.cm. of the serum killed the animals in twenty or thirty hours. With 10 c.cm. the animals lived twenty-two days, and with 12 c.cm. from thirty-five to forty-two days. Finally, 6 grams of serum of a goat which had received tuberculin and dead bacilli preserved the lives of the animals for from fifty to seventy days.

Maffucci and Di Vestea injected into sheep 456 mg. to 1670 mg. of bacilli killed by exposure to a temperature of 230° F. (110° C.) for twenty minutes. Living bacilli placed in contact for half an hour with the serum taken from these animals lost part of their virulence. Guinea-pigs which were inoculated with the mixture died far more slowly than those which received only the bacilli or those which received the bacilli and the serum separately. The latter, however, survived a little longer than the controls. It would seem, therefore, that under the influence of tubercular products there is formed in the organism a substance possessing the power of attenuating the action of tubercular toxins and even of the living

bacilli. In the latter case the two products must be previously mixed in vitreo.

3. *Mixed Method.* As early as 1892 Babes and Broca conceived the idea of preparing animals by means of injections of avian and human tuberculin, then by inoculating into them avian tuberculosis, and, lastly, human tuberculosis. The blood and the serum taken from dogs, rabbits, guinea-pigs, and cows treated in this manner neutralized tuberculin and prevented or cured tuberculosis in rabbits and guinea-pigs. The employment of these fluids produced good results, even in man; the fever ceased, the weight increased, and the cutaneous lesions, notably lupus, improved.

Antitubercular Serumtherapy in Man; the Serum of Maragliano. As has already been stated, several authors had obtained in man more or less marked improvements. Héricourt and Richet, as well as Boinet, utilized the serum of animals the resistance of which they thought they had increased. Paquin prepared a serum of equine origin. Bloch advocated the employment of the blood taken from the subcutaneous capillary network. The investigations of Maragliano placed the question upon a practical basis. In the first place this author established that tubercular cultures contained two kinds of toxic substances. Some of them, which are obtained by concentrating the culture at 212° F. (100° C.), are represented by proteins derived from the bodies of the bacilli. These are the substances found in Koch's lymph. The others, which are prepared by concentrating *in vacuo* at 86° F. (30° C.) and filtering the culture through porcelain, are particularly toxalbumins. This latter fluid manifests an action altogether opposite to that of the former. It kills the animals in a state of collapse, while tuberculin produces hyperthermia.

The animals which furnish the serum—goats, asses, and horses—are injected with progressively increasing doses of a mixture of three parts of the former and one part of the latter fluid. At the end of six months immunization is obtained, and three or four weeks after the last injection, venesection is practised. The serum is germicidal as well as antitoxic. It annihilates the toxic action of tuberculin. In a normal guinea-pig 1 gram of the serum neutralizes a fatal dose of tuberculin. In tubercular guinea-pigs, which succumb to a ten times smaller dose of tuberculin, it is necessary to inject 2 to 4 grams of the serum per kilogram of animal in order to save them. As regards tubercular human subjects, the dose of tuberculin which

causes fever is neutralized by 1 c.cm. of the serum. After they have been treated by the serum the tuberculous individuals become insensible to the action of tuberculin, even when use is made of doses ten times larger than those which, at the beginning, gave rise to reactions. The treatment consists in injecting into the patient 1 c.cm. every other day. In febrile cases in which no reduction in the temperature is obtained, the doses are increased to 5 c.cm. and 10 c.cm. If the fever disappears the dose is again reduced to 1 c.cm. This dose is to be employed if the febrile process is not arrested by higher doses. This treatment should be stopped in case of hemoptysis. A great number of physicians made use of Maragliano's serum, and the observations published are quite favorable to the method. The serum proved useful in 91 per cent. of the cases, and it proved curative in 16 per cent.

It is evidently too soon to conclude that Maragliano's serum is the true specific of tuberculosis. Numerous negative facts do not permit such optimism. The fact that may at once be recognized is that the medicine when employed in amounts indicated by the author does not seem to be dangerous and is at times efficacious. Perhaps the failures are due in part to the fact that in man the process is always complex. Besides tuberculosis, a whole series of secondary infections are to be combated. Here is the stumbling-block of antitubercular serumtherapy. The day we possess a serum capable of combating or destroying Koch's bacillus we shall still lack an infallible serum against tuberculosis, for, barring the cases of acute miliary tuberculosis, the infection is mixed, and, when it has reached the third stage, the patient that has pulmonary cavities and is suffering from hectic fever is a pyohemic rather than a bacillary sufferer. A whole series of serums, varying from one case to another, must be employed in a polymicrobic infection. The impossibility if not the dangerous character of such therapeutics is evident.

Typhoid Fever. It is not difficult to vaccinate animals against the bacillus of Eberth. This may be accomplished by employing the living microbes, as has been done by Beumer and Peiper, or by making use of sterilized cultures, as was advised by Chantemesse and Widal, Brieger, Kitasato, and Wassermann. The majority of authors to-day resort to the latter method. In order, however, to obtain an active serum, an exalted virus must be employed. The best means consists in making passages in series on animals, by favoring the development of the pathogenic agent by means of simultaneous injec-

tions of microbic toxins. These toxins are of two orders. Some are contained in the bodies of microbes. Funck makes use of these for immunizing animals. On the other hand, Chantemesse utilizes the poisons that diffuse into the culture bouillon. By means of a special medium he obtains a very active toxin which enables him to immunize horses, but the experiment is extremely long. It was only after two years of preparation that Chantemesse obtained a truly active serum. Klemperer and Levy, with the serum of dogs, and Börge, with a serum of sheep prepared by Beumer and Peiper, succeeded in shortening the morbid evolution.

Chantemesse, after establishing the immunizing and curative power of this serum upon animals, obtained very encouraging results in man. One-fiftieth of a cubic centimetre of the serum injected as a prophylactic into a guinea-pig confers immunity against a fatal dose of toxin. When he injected into guinea-pigs a dose of toxin which killed the controls in twenty-four or forty-eight hours, the guinea-pigs which subsequently received 25 cg. of serum four and even five hours after introduction of the poison usually resisted.

In man the treatment reduced the mortality to less than 6 per cent. The study of observations and of the course of the fever demonstrates the efficiency of the method more than statistics. An injection of from 10 c.cm. to 20 c.cm. of serum suffices to lower the temperature and cause the diazo reaction to disappear. The duration of the disease is shortened. Defervescence occurs early, and, contrary to what usually happens, the urine remains scanty for several days after the fall of the fever.

Infections the Agents of Which are Unknown or Not Well Known. We place in a separate group those infectious diseases the microbes of which are unknown, or little known, or have not been cultivated. Numerous attempts have been made in such cases, by employing the blood and the serum of convalescent men or of animals into which virulent products obtained from man had been injected.

Eruptive Fevers. The eruptive fevers, such as measles and scarlatina, are not transmissible to animals. Kélaïditès injected into heifers the blood and squamæ of scarlatinal patients. From 20 c.cm. to 30 c.cm. of the serum of animals thus treated sufficed to arrest the course of the infection. The same author prepared a serum against whooping-cough by injecting into dogs the bronchial and nasal secretions of patients. In most cases the serum of convalescents was made use of for therapeutic purposes. This is what we

accomplished in several cases of scarlatina. The method is quite simple and appears to be efficacious, as may be judged from the following observation:[1]

At 8 P.M. on June 17, 1896, a young man, fifteen years of age, was brought to our wards suffering from scarlatina. The attack had taken place forty-eight hours previously and had been ushered in by vertigo, headache, and sore-throat. At the time of his admission we were struck by the gravity of the general state. The patient was motionless and semicomatose. From time to time his limbs were shaken by slight convulsive movements, his face was drawn, his eyes fixed, and dyspnea was extremely intense. Sixty-eight respiratory movements a minute were counted and 120 regular and quite strong heart-beats. The skin was covered with a generalized scarlatinal eruption. The tongue was dry and the tonsils swollen and covered with a pultaceous deposit. After his arrival the patient voided a small amount of non-albuminous urine. Owing to the gravity of the general state our interne gave, at 10 P.M., a subcutaneous injection of 400 grams of salt-water; at 1 A.M. a bath was given at 82.4° F. (28° C.).

On the morning of the 18th the general state was about the same as on the previous evening. The patient was comatose, and his extremities were at times convulsed, the tongue dry, the temperature, taken every three hours, was reduced after the administration of the bath, then it rose and, in the morning, reached 105.3° F. (40.2° C.). The number of respirations was 68; the pulse did not exceed 120, but was extremely weak. The patient had voided no urine since the previous night.

A fatal termination seemed to be approaching. We resolved to employ serum treatment. A man convalescent from scarlatina was willing to furnish the blood. As, however, it was necessary to act promptly, we could not prepare serum. Hence, we decided to inject defibrinated blood. For this purpose we took a glass ball, and, after introducing into it a certain quantity of pearls, closed it with cotton. The ball was sterilized at 356° F. (180° C.). The vein of the convalescent was then opened and 100 grams of blood drawn. By gently agitating the ball the pearls separated the fibrin, and an aseptic fluid was thus obtained. These preparations had taken an hour. During this time the state of the young man had become still

[1] Roger. Quelques réflexions sur le traitement des scarlatines graves. Essai de sérothérapie. La presse médicale, 1896.

worse, and a fatal issue seemed imminent. At 11 A.M. we bled the patient and took from him 150 grams of blood. Eighty cubic centimetres of defibrinated blood taken from the convalescent were then injected beneath the skin of the abdomen.

At 4 P.M., when the author saw the patient, he found him sleeping and breathing quietly; he then awoke and, having made a few movements, the respiratory rhythm changed and assumed the type of Cheyne-Stokes. The pulse-beat was 120 and weak, although less so than in the morning. Prostration was less marked and the tongue had become moist. In spite of this notable amelioration of the general state, the temperature remained high and the patient passed no urine. He was then given a bath at 82.4° F. (28° C.). The temperature then began to fall. At 7 P.M. 400 grams of salt water were injected beneath the skin. At 8 P.M. he passed urine. At 10 P.M. the interne found the patient sleeping quietly, his pulse 100, respirations 25 per minute. On the following morning the patient was found completely transformed; he spoke easily, felt well, and asked for food. The tongue was desquamated but moist, and the eruption was pale, except in the lower extremities, where it was still marked. The pulse, 80 per minute, was still somewhat weak, but very regular, and the respiration 22. Finally, since 8 o'clock of the previous evening until 8 o'clock the next morning, the patient voided 1100 c.cm. of a dark red, non-albuminous urine. The temperature oscillated during the day around 100.4° F. (38° C.), and on the following day it returned to the normal in a definitive manner. On the following days nothing special was noted. The infection was shortened, and in so serious a case we have never seen so rapid a convalescence.

When recovered the patient told us that he did not remember his arrival at the hospital or the salt-water injection given him at that time. He remembered only the bath which had been given at night. This consciousness, however, had not lasted long, for the patient could not recall the bleeding nor the injection of defibrinated blood. He had come out of his comatose state later in the day. He clearly had kept the remembrance of my visit of 4 P.M. and all the events taking place after that time. These retrospective details are interesting inasmuch as they show the extreme gravity of the situation at the time of intervention. It may be said that our observation is too complex, since recourse was had simultaneously to several therapeutic methods. This mode of action renders demonstrations less exact, but it was the only one permissible. By studying the

evolution of the disease, however, it is possible to discern what is due to each procedure employed. Improvement began after the injection of the blood and, unless it is assumed that the change in the general state would have occurred even without intervention, which is among the possible events, the amelioration is to be attributed to the influence of the hemotherapy. The improvement thus started continued, owing to the auxiliary action of the bath and especially to the injection of salt-water.

The same hemotherapic method is applicable to measles. In four cases Weisbecker saw rapid arrest of bronchopneumonias of measles under the influence of the serum of convalescent individuals. These researches are the more important as they were made on very young children—*i. e.*, under particularly grave conditions. The rapid disappearance of the thoracic manifestations leads to the question whether bronchopneumonia is really, as is generally admitted, exclusively dependent upon secondary infection, or whether, as Dr. Lesage thinks, the principal agent of the disease plays a more important rôle in its development than is generally supposed.

Analogous methods have been employed against recurrent fever, (Gabritchewski), typhus fever (Lewaschew, Hammerschlag, v. Jaksch, Legrain), and acute articular rheumatism (Weiss). The observations are too small in number to justify discussion of these attempts at length.

Vaccine and Variola. Sternberg is to be credited with having demonstrated the properties acquired by the serum as a result of Jennerian vaccination. This author, whose investigations were confirmed by Kinyoun, recognized that a drop of vaccine when mixed with four drops of serum of a calf vaccinated for two weeks, loses, at the end of an hour of contact, the power of causing vaccinal eruption.

This was the first step in the way of serumtherapy. The authors, however, who attempted to immunize animals by means of the serum of vaccinated subjects obtained results which were not very satisfactory. We must come to the important work of Béclère, Chambon, and Ménard,[1] who demonstrated that the serum of a vaccinated calf when not taken during the virulent period—*i. e.*, from ten to fifteen days after vaccination—possesses, with regard to the inoculated vaccine, immunizing properties, provided very considerable amounts of

[1] Béclère, Chambon, and Ménard. Etudes sur l'immunité vaccinale et le pouvoir immunisant du sérum de génisse vaccinée. Annales de l'Institut Pasteur, January, 1896.

serum are introduced beneath the skin. It is necessary to inject an amount equal to one-hundredth part of the weight of the body, and even then the immunity obtained is incomplete. A great number of inoculations are ineffective. The eruptions which appear are rudimentary. However, the most important fact from a doctrinal standpoint is that the contents of these eruptions are not virulent. They cannot be employed to inoculate other individuals. The authors furthermore remark that the action of the serum depends rather upon the substances which are dissolved in it, since the effects are immediate. Twenty-four hours after the injection immunity is effected.

It is evident that serumtherapy cannot displace Jennerian vaccination, and this for two reasons: the amount of serum required is too great; the immunity produced is incomplete and is not permanent. Serumtherapy may, therefore, be resorted to only in those cases in which non-vaccinated individuals are found in contact with variolar patients, especially if they present at that moment some morbid symptoms announcing the invasion of variola. It would then be feared that vaccine would act too tardily to modify the organism in time. The serum is to be utilized under such conditions and, if necessary, an inoculation with the vaccinal virus made at the same time.

The authors, however, who studied the vaccinal serum, had another end in view. They looked for a remedy against variola. As early as 1893 Auché, and then Landmann employed human serum obtained from cured variola cases. They obtained no appreciable result. Landmann likewise failed with the serum of vaccinated heifers, while Elliot saw a patient recover without any cicatrices after the injection of 105 c.cm. In another case, which was a very grave one, 65 c.cm. did not prevent the fatal termination. According to Béclère, the failures are due to the fact that the amount of serum administered is too small. This author injected amounts far exceeding those employed in other diseases. He made use of doses equivalent to one-fiftieth part of the weight of the body in adults, and to the twentieth part in children. Thus, in a case reported by him, a woman weighing 70 kilograms (155 pounds) received 1560 c.cm. beneath the skin of the abdomen in one hour. This patient bore the injection well and rapidly recovered. Béclère, during the Marseilles epidemic, treated ten cases of variola. Three of them died; one of them, however, had from the beginning a hemorrhagic variola, the

other was a newborn suffering from athrepsia. We may add to the list a few cases treated by Dr. Béclère in our isolation ward at the Hospital of La Porte d'Aubervilliers, several of them with success.

Owing to his scientific temper, Dr. Béclère abstains from drawing any conclusions from his serumtherapy method. The facts are too small in number to enable one to form a well-founded opinion. There is one thing, however, that can meanwhile be affirmed, viz., that the method is harmless. The serum, even when administered in very large amounts, is borne perfectly. Hence, there is no reason for not continuing the experiments. Of course, the patients should at the same time be treated by the usual means, and the physician should be glad to find a useful auxiliary in serumtherapy. In view of the first results obtained and the recent investigations pursued by Dr. Courmont, we may conclude that the action of the vaccinal serum should be increased and rendered more energetic. Although the calves submitted to repeated inoculations do not seem to furnish a more efficacious serum, some results may, perhaps, be arrived at by modifying the mode of introduction and by injecting, for example, large amounts of vaccine into the circulatory system.

Hydrophobia. After the discovery of Richet and Héricourt, Babes pursued a series of studies on antirabic serumtherapy. Then followed Tizzoni, Schwarz, and Centanni, who added some important data to the controversy. In their first experiments Babes and Lepp recognized that a dog after having received for six successive days 5 c.cm. of blood of a vaccinated dog, becomes refractory to the inoculation of hydrophobia. The result is the same in rabbits. After allowing four dogs to be bitten by hydrophobic animals, the authors kept two of them as controls. These died within sixteen and twenty-eight hours, respectively. The other two received, for seven days, the blood of the vaccinated animals; one of them died tardily, the other resisted. This favorable action of the blood probably depends upon a power which may be demonstrated outside of the organism. Babes and Cerchez, and Tizzoni and Schwarz proved that when the blood or the serum of a vaccinated dog is left for several hours in contact with the virus of hydrophobia, the latter loses its pathogenic properties. This action seems to be due to a globulin which is soluble in glycerin, precipitated by the sulphate of magnesia and by alcohol, and does not pass through the membrane of the dialyzer (Tizzoni and Schwarz). By employing strongly immunized animals we may succeed in preparing a serum of very great activity. From this point

of view, the serum of Tizzoni and Centanni seems to respond to all requirements. It is prophylactic in the proportion of 1: 25,000 for an inoculation of hydrophobic virus practised twenty-four hours later; in other words, 0.04 c.cm. suffices to immunize a rabbit weighing 1 kilogram. The proportion falls to 1 per cent. for the fixed virus. From six to ten times larger doses must be employed in treating animals already inoculated. These doses, however, are not excessive, since, for a man, they would not exceed the amount of 20 or 25 grams.

It would, therefore, be advantageous to substitute serumtherapy for the Pasteur method in those cases in which rapid action is necessary. Such is the conclusion reached by various authorities who have studied this question, notably that of Babes, who, since 1891, has employed this therapeutic method with success in patients who had been bitten by hydrophobic wolves.

Syphilis. As all animals are refractory to syphilis, any species might be chosen for the first serumtherapy attempts. The dog, the sheep, the lamb, the calf, and the rabbit have been made use of. Their sera have increased the strength of patients and hastened cicatrization of rebellious ulcerations. This is practically the same effect as is at times produced by the serum of normal animals in tubercular ulcerations.

The evolution of the disease, however, did not seem to be in any wise influenced by these injections. A specific serum was, therefore, looked for. Pellizzari then tried the method which yielded results in other diseases. He injected the serum obtained from syphilitic individuals infected for a greater or less period of time. The results were insignificant, a fact undoubtedly due to the too small amount of antitoxin contained in the blood of a syphilitic. Hence, it was necessary to increase the therapeutic action of the serum. In this direction an attempt was made by G. Mazza, by injecting into animals from 10 c.cm. to 20 c.cm. of syphilitic blood. The author, however, does not seem to have pursued his researches with much persistence. The question was taken up by Drs. Richet, Héricourt, and Triboulet, who prepared their animals—dog or ass—with the blood of individuals presenting roseolar eruption. A few days later they bled the animals. Three patients were submitted to the treatment. In this manner they obtained a more or less lasting cicatrization of ulcerations which had resisted specific treatment, and in one case they saw the disappearance of certain symptoms which seemed to indicate the development of locomotor ataxia.

At that time Drs. Gilbert and Fournier published an important work in which they described various serumtherapy procedures. Into a newly infected syphilitic individual they injected within twenty days 204 c.cm. of serum taken from an old case of syphilis. Under the influence of this treatment the general state improved, the aching of the bones and head disappeared, and the eruptions gradually subsided. The results were fairly good, but not entirely satisfactory. Gilbert and Fournier then resorted to goats and dogs, into which they injected syphilitic blood in doses of from 170 to 180 grams, or else they introduced beneath the skin of the animals indurated chancres, papulæ, and, simultaneously, blood. The serum obtained from these animals served to treat seventeen patients. In a few cases the general state was ameliorated and the strength increased, but in several other cases the method completely failed. As the authors remarked, it is conceivable that there should be hesitation of judgment in the presence of such contradictory facts. From the perusal of published observations it seems that the serum derived from normal as well as from prepared animals may favorably modify the general state of the patients, stimulate the reactions of the organism, and favor cicatrization of atonic lesions. These results point out the indications of the method. In a general manner, however, serumtherapy is considerably inferior to the classical treatment. A similar conclusion is arrived at by Neumann, who reported a few hardly satisfactory attempts.

Prophylactic Injections of Serum. Prophylaxis or, if the author may say so, vaccination by serums, is superior to vaccination by attenuated microbes or soluble products, because it exerts an immediate action and does not cause the organism to pass through a preparatory phase during which its resistance is diminished. On the other hand, it is inferior, because the immunity which it confers does not last long; it is effective only for a few days or weeks. It may, therefore, be theoretically stated that it is useful to vaccinate individuals by means of attenuated or sterilized cultures in the presence of an epidemic or in view of a future contamination; but we must resort to the serum in case of urgency, especially when we fear that the subject may already have been contaminated. Prophylactic injections of serum have been employed in several circumstances, notably in puerperal women, in wounded individuals, and in those for whom the development of tetanus is feared; finally and particularly, in those who have been exposed to contamination by diphtheria. The

observations regarding diphtheria cases are sufficiently numerous to support a conclusion.

Roux is decidedly in favor of preventive injections. Behring is of the same opinion. He advises the introduction of a small amount of serum—1 c.cm. of the No. 1—and renewal of the injections every six weeks. Unfortunately, this practise does not seem to be sufficient. The amount administered is too small to obtain durable immunity. In order not to overload our work with statistics, we shall be contented with citing those given by Krasnobaeff. Out of a total of 1965 individuals preventively injected, there were 43 cases of diphtheria, three of which died. Considering the results obtained in children's hospitals in various countries, it is found that out of 344 prophylactic injections there were 7 cases of diphtheria, 3 of which proved fatal.

This gives a death-rate of 2.03 per cent. In these same hospitals in non-injected children the mortality is about the same, namely, 2.71 per hundred.

It would be an easy matter to report a very great number of cases in which prophylactic injections have failed to prevent either the development of the disease or a fatal termination. They do not, therefore, seem to be very efficacious. Their employment might, nevertheless, be recommended if the injections were absolutely harmless. Such is not the case, however, as we shall see in the following chapter. And it is no wonder, then, that the prophylactic method does not seem likely to become generally adopted. The author does not believe that physicians, experimenters, or students connected with diphtheria wards receive from time to time inoculations of the serum as a preventive measure or give such injections to their families. They are not to blame if they do not intervene before the disease is manifested, because it is not wise to run the risk of the various serum-therapy accidents with a view of avoiding an eventual contagion, which is fortunately of very rare occurrence. Although it may be resorted to under certain circumstances, for instance, when epidemics attack a college or a ward of a hospital, or in families in which one child has already died and the parents fear for the surviving children, it does not seem that the method should be currently practised, for there would be no reason for not regularly injecting in the near future with various prophylactic serums with that of typhoid fever as well as of erysipelas and pneumonia. It would be necessary to frequently repeat these injections, since the immunity thus conferred is transi-

tory. This would tend to expose one's self to the various accidents of which we are now about to speak.

Accidents Ascribable to Serumtherapy. We have thus far reported therapeutic attempts and results; we have studied the action of serums regardless of the modifications and accidents which may be caused by their use. We must now consider this important question which has given rise to a great number of contradictory contributions. In this connection we may refer to an excellent résumé, namely, the thesis written by Dr. Poix[1] upon our advice. It is a very complete monograph, from which we shall borrow a good many facts.

Cutaneous Manifestations. Abscesses. Serum injections may produce abscesses. This is not, however, an accident due to the method. It is at present well demonstrated that the process is one due to carelessness, to insufficient disinfection of the skin and instruments, or to an alteration in the serum. Exception is to be made only with regard to the antistreptococcic serum obtained from animals immunized by means of living cultures. The living microbes may then be found in the fluid. We have found such to be the case in several instances and recognized that the streptococci had preserved a certain degree of virulence. On the other hand, numerous observations made upon man prove that these injections may give rise to abscesses, phlegmons, lymphangites, or erysipelas, which are at times sufficiently grave to cause serious anxiety. It is not to be concluded, however, that the antistreptococcic serum thus prepared is to be abandoned. In order to avoid accidents, it suffices to take the blood a longer period of time after the last injection of the culture or to filter the serum through porcelain. These precautions are evidently quite elementary, but they must not be overlooked when a product is destined to be used in the treatment of patients.

Exanthemata. Exanthemata are far more important. They are not like abscesses, due to defective preparation; they depend upon the action of the serums themselves, and seem, therefore, to be unavoidable, as they are caused by normal serum as well as by various medicinal serums. They generally make their appearance three or four days after the injection; at times on the tenth or even twentieth day. The age of the subject does not seem to exert any influence,

[1] Poix. Recherches critiques et expérimentales sur le sérum antidiphtérique (son action sur l'organisme, ses accidents). Thèse de Paris, June, 1896.

and, what is more difficult to explain, the accidents are in nowise related to the doses introduced; 1 c.cm. or 2 c.cm. may give rise to grave phenomena, while 10 c.cm. or 20 c.cm. of the same sample may be well borne. All seems to depend upon individual predisposition. In certain cases the manifestations consist simply in the appearance of various eruptions, such as urticaria or erythema. In other instances there is, in addition, fever and arthropathies. Finally, in certain rare instances, albuminuria, hemorrhages, gastrointestinal disturbances, etc., appear after the eruption.

The frequency of serumtherapy eruptions varies greatly from one time to another, which is partly due to the fact that all horses do not furnish identical serums. There are some the sera of which almost invariably cause eruptions, while others hardly ever produce any. It seems that accidents are less frequent when the animals are submitted to fasting before blood-letting is practised. It may, nevertheless, be remarked that the eruptions appear in 14 per cent. of the cases. This is the figure given by Dubreuilh, who reviewed 1946 observations. The same author ranges the various eruptions according to their frequency in the following manner: urticaria in 156 observations; scarlatiniform erythema, 46; polymorphous erythemata, 31; rubeoliform erythemata, 11. These eruptions generally make their appearance from the fifth to the thirteenth day after the injection. They quite frequently begin at the point of inoculation, invade more or less the rest of the skin, but, in general, do not involve the face. Urticaria, the most frequent eruption, presents nothing peculiar in its evolution. It is benign and transitory. As their name indicates, the rubeoliform eruptions have the aspect of measles, with which they might be confounded if the skin only was examined. At times pure, they may often be mixed with scarlatiniform eruptions. The latter generally occupy the back, the flexor surfaces of the extremities, more rarely the thorax, and almost never the face. They are in many cases pruriginous, whether urticaria coexists or not. As a result of these eruptions, there is usually a slightly marked desquamation.

Under the name polymorphous erythemata authors have sometimes described eruptions characterized by mixture of several eruptive types, sometimes eruptions in which certain elements become bullous. In some instances the eruption assumes a hemorrhagic character (Mendel) or that of purpura (Moizard and Perregaux). The cutaneous manifestations are generally transitory. They last from

three to six days, but relapses occur in a certain number of cases. They are often attended by arthropathies.

Arthropathies. Post-serumtherapy arthropathies are simply characterized by particular pains, in most cases coincident with eruptions, and never ending in suppuration. The only observation of suppurated arthritis, that of Broca, is so complex that it cannot with certainty be attributed to the serum injected. The articular symptoms usually occur in the knee-joint and ankle-joint, and are often attended by muscular pain or neuralgia, at times by edema in the back of the hands and feet. These arthropathies commonly disappear with the eruptions.

General State. Beside the eruptions and articular phenomena, the patient also presents a number of general manifestations. Fever occurs and sometimes reaches 104° and even 105.8° F. (40° to 41° C.). There are digestive and urinary disturbances. These manifestations last but a few days, but the patient remains pale and tired. In some cases, however, the disorders may last for several weeks. We must now consider in a special manner two series of phenomena which may occur separately: hyperthermia and urinary disorders.

Fever. Dr. Variot was the first to call attention to the fever caused by the injection of serums. He proved its existence by comparing a great number of fever charts. We are able to confirm his observations on this point, for patients who arrive at our hospital ward devoted to adults are generally apyretic. It is, therefore, very easy to observe in them the occurrence of hyperthermia and to refer it to its true cause. The febrile movement, which is often of a slight and transitory character, may also be observed when serum is injected as a prophylactic into normal subjects. The temperature rises a few tenths of a degree or even two degrees. At the same time the pulse is accelerated and sometimes becomes a little irregular. These thermal elevations, which occur a few hours, sometimes a day or two, after the injection of the serum, are not to be wondered at. The same phenomena occur in consequence of injections of normal serum. This fact has been observed in man as well as in animals. The hyperthermizing action of normal serum had been noted by ourselves, then by Drs. Mairet and Bosc; but we had practised intravenous injections. Poix made a very careful comparative study by injecting normal as well as antidiphtheritic serum into rabbits. These injections were made beneath the skin, and in both cases gave rise to very decided hyperthermia.

Modifications of the Urine. Injections of serum seem to modify in a variable manner the quantity of urine voided. Some authors have noted a considerable diminution, others an increase, still others no change at all. These contradictory results probably depend upon the state of the individual under observation. What seem to be more important are the qualitative modifications of the urine.

The serum causes an increase in the excretion of urea (Mya, Mongour, etc.). Hyperazoturia generally lasts twenty-four hours; then the amount of urea diminishes and returns to the normal. At the same time there is a notable increase of phosphates and a slight diminution of chlorides. Karlinski, experimenting upon himself, found that a subcutaneous injection of 10 c.cm. produced no fever and no urinary modifications. This dose, however, is rather too small for an adult. By injecting larger amounts he noticed the appearance of urticaria and an increase in urea, uric acid, and creatinin. These urinary modifications lasted three days, but they did not depend upon the antitoxin, since the author observed analogous disorders with the serum of a normal goat.

Investigations pursued upon animals fully confirm the results obtained in man. Our experiments[1] and those of Poix prove that injections of serum produce slight polyuria, an increase in urea and phosphates, and a diminution in chlorides. It is to be noted, however, that Poix has perfectly demonstrated that these various modifications are likewise produced under the influence of normal serum.

All that remains to say concerning the usual modifications of the urinary secretion is that, according to Heckel, peptonuria is constantly observed, and that, according to Le Gendre, urobilinuria may be observed. It now remains to examine with particular attention a more serious accident with regard to which there is no general agreement. We refer to albuminuria.

Albuminuria, Nephritis. The most varied opinions have been advanced concerning the disturbances which the serum engenders in the kidneys. As a matter of fact, clinical observations are always very complex, and it is evidently quite difficult to determine the rôle which is to be respectively attributed to the principal infection and to the secondary infections in addition to those produced by the serum. Some authors have, therefore, thought, and with good

[1] Charrin and Roger. Action du sérum antidiphtérique sur la nutrition. Soc. méd. des hôpitaux, December 14, 1895.

reason, that it was necessary to study the question by experimentation upon animals. Unfortunately, the results obtained have been quite contradictory. Vissman found that the kidneys were congested, and he discovered by microscopic examination that the vessels were overloaded with blood and the cells of the tubuli filled with refractive granulations. The histological examinations, however, were made upon fresh tissues, because the author believed that reagents would prevent him from seeing the lesions. In the experiments of Kossorotoff the alterations were more marked. There was hyperemia in the liver and kidneys, and cloudy and granular degeneration of the cells. The results obtained by Von Kahlden were altogether different. A rabbit received 16 c.cm. in four days; a guinea-pig received, in the same period of time, 12 c.cm. Microscopic examination revealed no lesion in the kidneys and myocardium. Nor did Zagari and Calabrese observe any renal lesions in the animals which had received serum. Poix injected into rabbits from 5 to 15 c.cm. of antidiphtheritic serum; two animals received 25 c.cm. in three doses. Histological examination, made by Dr. Comte, revealed no appreciable alteration.

It seems, therefore, that the serum injected into rabbits and guinea-pigs produces no renal alterations. This result evidently has considerable value, but its importance should not be exaggerated. It must not be concluded that the serum is incapable of producing any alterations in man, since animals possess, in this respect, far greater resistance. All experimenters who have attempted to create nephritis or albuminuria in animals know how difficult it is to succeed if brutal measures are not resorted to; they also are aware with what facility the manifestations subside and disappear. On the other hand, it should not be overlooked that different animals react differently against various serums. It seems, for example, that the rabbit is far more sensitive than man to bovine serum; it may, however, be the reverse with regard to horse serum. Let us now see what occurs in man. Martin and Chaillou think that the serum hinders the action of the toxin upon the kidneys and considerably diminishes albuminuria. This conclusion may be admitted with certain reservation. It is possible that the serum, when injected at the beginning of the infection, by arresting the toxi-infectious process, prevents the ulterior alteration of the kidneys; its action is like that of salicylate of soda, which, by opposing the evolution of acute articular rheumatism, diminishes the frequency

of endocarditis. This, however, is only a theoretical deduction or conception, since accurate information on this subject is lacking.

When albuminuria exists the serum does not seem to ameliorate it. It is not strange that such should be the case. The serum is no more capable of curing a renal lesion than salicylate of soda is of curing rheumatic endocarditis. The anatomical alteration, when once established, continues its evolution; the serum is capable only of preventing its development. Some authors, however, go further and accuse the serum of aggravaitng pre-existing lesions, a question very difficult of solution. It is evidently necessary to resort to experimentation to determine the result of the injections of serum into animals in which renal alteration has previously been created. This question was investigated by Ritter, who noticed that the serum, when injected into animals recovering from artificial albuminuria, causes reappearance of albumin in the urine. On the other hand, Zagari and Calabrese injected serum into individuals suffering from chronic nephritis, and did not observe any increase in albuminuria. The question, therefore, requires more thorough study.

There remains a last group of cases in which the serum seems surely to cause albuminuria. Such is the case when remote post-serumtherapy symptoms supervene. Several days after the injection of the serum, when eruptions, articular symptoms, and febrile movement occur, albuminuria also may be observed. In this instance it is quite difficult not to attribute the urinary disorder to the influence of the serum; for, in cases of diphtheria treated by the usual procedures, albuminuria seldom makes its appearance so tardily. On the other hand, the symptom forms part of a whole series of disturbances constituting a sort of clinical entity; there is no reason for separating it from the rest. In most cases, these albuminurias are transitory. In some instances, however, they have proved quite serious. Elsewhere, the renal disorder has been expressed by anuria, and in other cases by a hemorrhagic nephritis. The latter manifestation seems to us interesting because, in the genesis of post-serumtherapy accidents, hemorrhages play an important rôle. Experimenters had already observed multiple hemorrhages in consequence of the introduction of foreign blood or serum into animals.

Hemorrhages. Besides hemorrhagic nephritis and cutaneous hemorrhages, notably purpura, the serum has sometimes given rise to epistaxis and uterine hemorrhages. D'Astros made a careful

study of the action of serum upon the uterine functions, and found that when it is applied at the time of menstruation it increases the flow; during the interval it brings it on. Metrorrhagia appears the day following the injection, or later. It generally coexists with a cutaneous eruption. However, in a case in which the serum was injected into a pregnant woman, the progress of pregnancy was in nowise disturbed.

Modifications in the Blood. It is difficult to say whether hemorrhages following serumtherapy result from an action exercised upon the vasomotors or upon the blood itself. It is known that the serum produces some interesting modifications in the constitution of the blood. It diminishes leucocytosis. This is not a common action engendered by any serum whatever. The researches of Ewing clearly demonstrated that it is due to a specific action of the antitoxin. He proved it by experiments upon animals and observations in man. Hypoleucocytosis lasts twenty-four to forty-eight hours. It is especially the mononuclears and, among the polynuclears, those that are stained with difficulty, that disappear. The polynuclear cells that are well stained do not present any modifications. It is probably a process of negative chemiotaxis, which causes such an accumulation of leucocytes in the viscera that it has been questioned whether it is not dangerous.

Another interesting phenomenon is the fact that the serum increases the aptitude of the leucocytes for taking up dyes. Toxins have a reverse effect. In those cases in which the injection of serum does not cause the reappearance of a normal tinctorial reaction in the leucocytes, prognosis may be considered as fatal. If these facts were confirmed they would constitute a very simple means of foretelling the evolution of diphtheria. For the time being we must be contented with the fact that the number of leucocytes undergoes variations. On this point the investigations of Schlesinger have confirmed those of Ewing: Out of twenty-four children suffering from diphtheria, in twenty-one the injection of serum first caused leucocytosis to disappear; this was followed by a slight secondary leucocytosis.

These results are evidently interesting in view of the important rôle which the leucocytes play in the protection of the organism. It is for this reason that authors have devoted special attention to wandering cells. It is to be regretted, however, that they have neglected the red globules. The question was taken up only by

Zaggari and Calabrese, who observed a diminution in the number of red corpuscles and of their richness in hemoglobin. These researches are particularly welcome for the reason that serum has been held responsible for some grave and rebellious anemic conditions. Children who had received it as a preventive are said to have for months remained pale, weak, and to have presented furuncular eruptions, which means a marked disturbance in their nutrition and development. This conclusion finds support in Dr. Arloing's investigations. This author studied the development of young guinea-pigs into which he daily injected small amounts of normal or antidiphtheritic serum. While the controls increased 34 per cent. of their initial weight, the animals which received normal as well as immunizing serum increased only 19 or even 16 per cent. The foreign serum thus exercises a harmful action, and the longer the serum is administered the more marked is this action. Of course, the quantities introduced were relatively more considerable than in the case of the child, but we know how resistant animals are. Without producing such harmful results, they are bad enough if only nutrition is disturbed and development hindered.

Other Accidents Ascribable to Serum. Other disorders attributable to the use of the serum have been observed in the course of post-serumtherapy syndrome, coincidently with eruptions and arthropathies. These disturbances consist in vomiting, profuse diarrhea, sometimes dysinteriform and sanguinolent diarrhea, swelling of the lymphatic glands and spleen, and, finally, cardiac disorders. The latter seem to be quite frequent, at least according to observations published in foreign countries.

Baginsky, who later on changed his opinion, Hunnius, Schroeder, and Springorum dwell upon cardiac arythmias, tachycardia, and *bruit de galop.* They likewise noted edema of the extremities, which indicates considerable weakness of the heart, and reported observations in which these various disturbances were quite serious and alarming. In a case concerning a young woman twenty years of age we observed some interesting nervous manifestations. In taking care of a three-year-old child suffering from diphtheria she had been bitten by the child and received two small abrasions on her middle finger. On the following day, the physician fearing the development of cutaneous diphtheria, hastened to inject 40 c.cm. of serum into the young woman, and sent her to our hospital. The wounds presented a good appearance and seemed in nowise diph-

theritic. For greater safety, however, cultures were made, which demonstrated the presence of no other microbes than the staphylococcus albus. Eight days later the symptoms of serum intoxication appeared, with fever progressively attaining 100.4° and 102.2° F. (38° and 39° C.) and articular pains. Two days after, this woman had, for the first time in her life, a well characterized attack of hysteria. From that moment on a series of neurotic manifestations appeared. First, convulsive attacks which recurred for three days in succession; then the patient became indifferent to everything about her, hardly replying to questions. The temperature oscillated around 104° F. (40° C.), and pulse 120 per minute; the tongue was dry. A few days later she suffered from anuria for forty-eight hours; then she had mutism for two days; after that the patient fell into an ecstatic state which lasted for a week. A month after the beginning of the disturbances she recovered.

It might be supposed that in this observation the question was one of traumatic hysteria, excited by the biting. The appearance of nervous symptoms forty-eight hours after the beginning of the fever caused by the serum, however, seems to indicate that it was a case of toxic hysteria and that the injection of the serum had been the cause of the manifestations.

Prognosis of Serumtherapy Accidents. We have above described the phenomena which may be attributed to serumtherapy. These unfavorable symptoms have been observed mostly in consequence of the use of antidiphtheritic serum. This is due simply to the fact that this serum is the only one currently employed, since it seems to be well demonstrated that the majority of these phenomena are not due to the antitoxin, but to an action possessed by all foreign serums.

An injection of serum almost always gives rise to a reaction, such as transitory elevation in the temperature, which, in most cases, hardly deserves the name accident. This reaction, however, may acquire alarming intensity in certain subjects who are already sick. This may occur notably in tubercular patients. Roux and Variot agree that the serum does not produce good results in this disease; it produces certain disturbances, and such is the opinion of several authorities. The injection of serum gives rise to a congestion just like an injection of tuberculin. In several personal cases, one of which was reported in Poix's thesis, we found that the injection of 20 c.cm. of serum caused a notable elevation in the temperature

and aggravated the general state of the patient. In the case published by Poix the patient died seven days later, and the necropsy revealed advanced tubercular lesions. It is difficult to say what the respective rôle of tuberculosis, of diphtheria, and of the serum had been in this fatal termination. We believe, however, that in cases of tuberculosis, at least of adults whose lesions are well pronounced, it is necessary, if diphtheria is not too grave, to abstain from injecting serum and have recourse to simple local treatment.

Barring this particular case, truly serious accidents are those which constitute the tardy syndrome. While in most cases the phenomena are transitory and in nowise disquieting, they at times last for four and five weeks. In other instances terrible manifestations, such as anuria and collapse, have been observed (Thibierge). It is true, however, that except in a few cases the patients have generally recovered.

We here arrive at a much disputed problem. May death result from serumtherapy? We may recall the communication of Moizard and H. Bouchard[1] and the bitter discussion to which it gave rise. Guinon and Rouffilange[2] published an analogous case, and others may easily be found in foreign literature. It is true that several of these cases cannot bear criticism; such is notably the strange observation of Langerhans' boy. There are others, however, which cannot be easily explained away. One such interesting case is that related by Izor Alfoldi: Forty-eight hours after an injection of 2 c.cm. of Behring's serum No. 1, administered as prophylactic, a three-year-old child developed fever. The temperature rose to 104° F. (40° C.) attended by lumbar pains and much albuminuria. On the third day the child had nausea, an eruption of petechia on the body, and died the fourth day. The mechanism of these phenomena is open to discussion, but it is hardly possible not to admit a relation of cause and effect in the fact of so typical a syndrome appearing a few days after an injection of the serum in a child which until then was perfectly healthy. It seems to me that nothing is gained by systematically explaining away such observations or interpreting them in such a manner as to clear serumtherapy of

[1] Moizard and Bouchard. Un cas d'angine non-diphtérique, traité par le sérum, suivi de mort. Société médicale des hôpitaux, July 5, 1895.

[2] Guinon and Rouffilange. Un cas d'angine membraneuse traité par le sérum de Roux; mort avec anurie et convulsions urémiques. Revue mens. des maladies de l'enfance, March, 1895.

all responsibility. It is better to acknowledge frankly that serums may produce some accidents. At all events, what medicine may be considered perfectly harmless? Is there any active substance, even chemically well defined, which never occasions any disturbances? Only those who endeavor forcibly to transfer mathematical data into the domain of biology can imagine that it is possible to fix immutable doses and establish a formula in which dangerous and fatal doses will be precisely indicated. In reality, facts are more complex. The experimenter himself must take into account the individual peculiarities of animals. As regards serums particularly, individuals of the same race, age, and weight react very differently against the same fluid. The investigations of Hayem, Mairet, Bosc, and of ourselves, demonstrated this fact beyond all dispute. The same is undoubtedly true of man, whose idiosyncrasies are far more marked. In proportion as the nervous functions are more perfected and complicated the results become less and less fixed, while sensitiveness to toxic agents becomes more and more pronounced.[1]

We should say that the disturbances, at any rate exceptional, which may occur in consequence of serum injections, must by no means restrict the employment of the method, but impel experimenters and clinicians to perfect it. Since most of the dangerous phenomena are due to the serums, and are independent of the antitoxin, the efforts of experimenters should be directed to the preparation and isolation of the active substance. The day when we possess a product which, if not pure, is at least freed from a great number of useless or harmful substances, decided progress will have been accomplished. Meanwhile, we are fortunate to possess a therapeutic method which has notably reduced the death-rate.

Causes and Mechanism of the Accidents. It is impossible to argue to-day that the disturbances following serumtherapy are due to diphtheria itself, or that they are produced only after such grave cases of diphtheria which, without the new treatment, would terminate in death. The appearance of similar manifestations in healthy subjects who have received preventive injections, or in persons suffering from non-diphtheritic anginas, suffices to invalidate this

[1] There will be found a number of facts demonstrating individual sensibility to toxic agent in the author's article, "Intoxications." Traité de pathologie générale, Paris, 1895, vol. i. p. 849.

explanation. On the other hand, identical disturbances, not only eruptions, but articular symptoms, fever, gastric disorders, and hemorrhages occur in consequence of injections of normal serums. It is not, therefore, the antitoxin that is responsible for the disorders but the introduction of a foreign serum.

It cannot be objected that nothing of the kind occurs when the blood of horses is injected into rabbits, for it is possible, with other serums, to obtain results comparable to those occurring in man. If the blood of dogs is introduced into rabbits, albuminuria and hemorrhages often appear. The results are still more interesting when cow's serum is injected into dogs. According to Dr. Hayem, considerable individual differences, resistances altogether dissimilar from one individual to another, are observed. The same injection may produce nothing in one dog and cause in another, apparently identical with the first, hemorrhages, anuria, or albuminuria, and even death. This is, therefore, as far as is possible in experimentation, the reproduction of what occurs in clinical experience.

These facts will serve to refute a very ingenious theory advanced by Sevestre.[1] This able clinician divides serumtherapy disturbances into three groups: Those immediately following the injection of the serum, viz., elevation in the temperature and acceleration of the pulse—accidents which, like the preceding ones, are due to the serum. Such is flying urticaria, appearing from the fourth to the sixth day. Finally, the tardy disturbances, namely, those of a serious character, including various exanthemata, albuminuria and articular disorders. Regarding these Sevestre does not admit that they are due to the action of the serum, but he attributes them to the influence of streptococci, viz., to secondary infections. His theory has not many adherents. It seems to me hardly acceptable, for, as it has already been stated, the serum causes the same disturbances in individuals suffering from chronic infections, and in normal subjects. All that may be admitted is that by disturbing the organism the serum may favor the development of microbes until then inoffensive. It may also be admitted that certain symptoms are of an infectious order. For instance, dysenteriform diarrheas may be due to exaltation of intestinal bacteria. Analogous symptoms are observed in the course of a great number of intoxications. A well-known instance is mercurial stomatitis or

[1] Sevestre. Des accidents imputables à la sérumthérapie ou au streptocoque dans la diphtérie. Soc. méd. des hôpitaux, July 19, 1895.

enteritis. The microbes of the mouth and of the intestine cause these lesions, but their action is rendered possible through the intervention of mercury. Mercurial stomatitis and enteritis must remain among toxic affections, and the same is true of post-serum-therapy accidents.

Among the substances contained in the serum, it is the albumins that are probably the active agents. The numerous experimental investigations which have shown the dangers of heterogenous transfusions have demonstrated that all the disturbances depend upon albuminoid matters. On the other hand, the researches of Mairet and Bosc proved that heating the serum between 132.8° and 138.2° F. (56° and 59° C.) may abolish its coagulating and globulicidal properties, but its toxic action remains intact. Therefore, the blood does not produce disturbances by destroying the globules of the transfused individual or by causing coagulation in the vessels.

For the time being we are unable to further elucidate the mechanism of the phenomena. We do not know whether the direct action of the foreign albumin or that of the products resulting from its decomposition are responsible, or whether we must admit the secondary formation of noxious products within the organism.

Mode of Action of Therapeutic Serums. After all the developments above presented regarding the chemical modifications occurring in vaccinated animals and concerning the special characters of their serums, the mode of action of the latter will be briefly considered.

Two principal theories have been advanced: One of them endeavors to reconcile the results of serumtherapy with the exclusively phagocytic doctrine; the other seeks for a purely humoral explanation. In the first place, it is supposed that therapeutic serums act by stimulating the activity of the wandering cells and by increasing their phagocytic power. If, in certain instances, the serum acts more energetically when injected into the adjacent parts of a local lesion, this is due to the fact that it exercises a positive chemotactic action; it calls out, so to say, and attracts the leucocytes to the point threatened. The active substance would then deserve the name *stimulin*.

Several objections could be raised against this hypothesis. By means of very ingenious experiments, Denys and Leclef demonstrated that, in rabbits vaccinated against the streptococcus, the leucocytes are not more active and aggressive than in normal rabbits.

Whether or not the animals are refractory, the leucocytes do not attack the virulent microbes; they seize only those which have been altered by the curative serum. These researches bring us to the theory which we have always advocated, viz., that immunity is the result of the co-operation of two principal factors: the plasma or the serum, which temporarily weakens the microbe, and the leucocyte, which picks up and destroys it. Were it not for the previous action of the fluids the phagocytes would be powerless and the infection would develop, and without the terminal action of the phagocytes the microbes, which were temporarily weakened, would finally prove victorious, as they do *in vitro;* the infection would be delayed but not arrested.

Let us apply these data to serumtherapy. By injecting the prophylactic or curative serum, we assist an organism which secretes antibacterial or antitoxic substances; since from the very beginning of the infection, or at least in some cases, the organism reacts against the microbe and endeavors to oppose it by substances which hinder its development. This protective secretion may be insufficient or tardy. We then come to the assistance of the struggling economy by furnishing it with substances formed in another organism. If the animal furnishing the blood is endowed with an immunity just sufficient for itself, its fluids will prove to be of moderate activity and the result will be almost negative. If, on the contrary, the animal is hypervaccinated, its fluids will contain an excess of protective substances, and the small amount injected will contain a sufficient quantity of antibacterial or antitoxic matters to favorably modify the morbid evolution.

Serumtherapy is, therefore, nothing else than a variety of antiseptic or antidotal medication. In the case of an antibacterial serum, serumtherapy introduces into the organism a specific antiseptic which hinders the vegetation and activity of the microbe. When the serum is antitoxic it introduces a substance which affects the cells of the patient, increases their resistance or prevents their impregnation. While the theory of stimulins may be comprehended when we consider the struggle against living bacteria, it is no longer intelligible when we consider the antitoxic rôle of serums. In fact, the experiments of Chatenay and Metchnikoff demonstrate that the number of the leucocytes diminishes when the animal succumbs to an intoxication, and that it increases if the animal is vaccinated and rendered resistant. Must it be concluded that, in the latter instance,

the leucocytes pick up the toxic substances, and must we thus extend to all the poisons the theory which some authors endeavor to establish concerning peptone? Such conclusions seem to be premature. To deduce such an important action from the simple fact that the leucocytes increase in number when a toxic substance is injected into a refractory animal seems to us to make too much of such a result. Before admitting or rejecting the hypothesis we must demand experimental facts, and especially a careful demonstration of the rôle played by the antitoxic functions of organs in vaccinated animals. Serums have such an important specific action that no one has given any attention to the other effects which they may produce in the organism. In order to completely appreciate their mode of action and explain certain cases in which a serum has acted against an infection of another nature, it must be remembered that the normal serum or even saline solutions may very favorably modify the course of various infectious or non-infectious diseases. We have already stated that the serum of certain animals is capable of favoring cicatrization of the most varied ulcerated lesions, notably syphilitic and tubercular lesions. Reinach tried in cholera infantum the serum of cows or horses, of which he injected from 10 to 20 c.cm. Out of twenty-five children thus treated only four died, and these suffered from pneumonia. In consequence of the injection, the pulse improved, cyanosis disappeared, and the extremities became warm. These good results are probably due, at least in part, to the nutritive value of the serum. According to this author, 20 c.cm. of serum correspond to 150 grams of mother's milk. It may be asked, however, whether the serum of animals, like saline solutions, does not exert an indirect action upon infections by modifying the state of the nervous system. The results obtained in the treatment of neurasthenia and the modifications produced in the arterial tension give a certain value to this hypothesis. These secondary influences may, of course, be ignored when we consider the action of specific serums. They are interesting only when we look for an explanation of the favorable effects obtained with such serums as are of moderate activity or which are obtained from normal animals.

Conclusions. In spite of the numerous investigations to which serumtherapy has given rise, we must acknowledge that it has not given undeniable practical results except in diphtheria. Even in this instance its efficacy is not so great in man as would be expected

from experiments pursued upon animals. The same remark is applicable with more force to other serums, all of which are capable of saving laboratory animals experimented upon and so often fail when tried on patients. This divergence between clinical and experimental results may readily be explained. The animals upon which experiments are pursued have been made ill by artificial means. Consequently, they were in a state of perfect health and in nowise disposed to be invaded by the infection. It was necessary to overcome their resistance brutally, and this unexpected arrival of microbes aroused immediately a prompt and vigorous reaction on the part of the organism invaded. On the other hand, the artificial disease is simpler, since it remains for a long time monomicrobic. Lastly, the treatment is applied in due time. A few hours, one day at the latest, after the inoculation intervention takes place in the first stage or even during the stage of incubation, while no morbid symptom has as yet expressed or revealed the invasion of the organism. In the case of man, however, the situation is altogether different. Except in rare instances, infection is not inoculated. Even in cases of traumatism the microbes are introduced in too small numbers to admit comparison with what occurs in the laboratory. If, therefore, disease is produced, it is due to a morbid predisposition, a previously debilitated state of the organism; its resistance was not artificially overcome in a brutal manner, but was progressively reduced by a series of preparatory conditions. Hence, when the microbe penetrates, reaction does not occur immediately, and is often incomplete or insufficient. On the other hand, the disorders which have prepared the development of the infection or the previous diseases, of which no apparent traces are presented by the subject at the moment of the attack, may have produced more or less profound visceral lesions which added their unfavorable influence to that of the infectious agents. Finally, the natural disease is not so simple as the artificial, for it is seldom monomicrobic. Several bacteria are almost always called into play, and thus modify the clinical course and increase the complexity of each case.

Hence, when we intervene by the serumtherapy method we face a disease dependent upon a series of various causes and the evolution of which is advanced, for a whole period of incubation and of prodromes has elapsed during which there has been no clear diagnosis of the nature of the infection. When the symptoms are clear and the diagnosis is established it may be too late to intervene. Such

is the case in tetanus. If there is yet time, the physician hesitates to apply new methods, and thus there is a delay which sometimes renders intervention useless. Let us suppose that action has been taken in due time, from the beginning of the disorders, are we sure of obtaining favorable results? Evidently not. The serum may combat bacterial intoxication, it may oppose the development of the microbes, it may neutralize their products of secretion, but it can accomplish nothing against concomitant autointoxications. The organs altered by previous diseases or by the present malady can no longer fulfil their functions in transforming or eliminating the toxins of cellular origin. On the other hand, it is to be remembered that there is an exaggerated production of poisons resulting from the nutritional disorders engendered by the disease. In view of these facts it is impossible, even when infection is monomicrobic, to draw conclusions from animal to man. Hence, serums succeed better in laboratories than in clinical experience, and, for this reason, old therapeutic methods should not be abandoned.

Under the influence of the enthusiasm which was aroused by antidiphtheritic serumtherapy, many believed that traditional therapeutics had served its time. Many believed they perceived the dawn of a new era when medicine would be simplified in a marvellous manner: no more auscultation, no more examination of patients; it would suffice to look for the pathogenic microbe and immediately inject the corresponding serum. These ideas, which were sustained by some eminent scientists, do not conform to the reality. To thus exaggerate the value of even such a magnificent method tends to bring it into discredit and to expose one's self to cruel disappointments. This medication of equation, to use an expression of Landouzy, will not succeed in therapeutics any more than elsewhere. Biological phenomena, especially pathological manifestations, are too complex to be modified by simple and uniform procedures. Serumtherapy is not destined to do away with the other methods. It must simply be considered as a new means to be employed concurrently with others. In the case, for instance, of a woman suffering from puerperal fever, whatever may be our confidence in serumtherapy, we should never resort to an exclusive method. We must continue to practise curettage, intra-uterine irrigations, and prescribe cold baths, being convinced that it is necessary to employ multiple measures of various effects in order to combat multiple phenomena of various origins.

While we cannot say too much in approval of the efforts of those pursuing researches upon specific serums, we must, in the interest of clinical experience, protest against the exclusive employment of laboratory methods. We have endeavored to show why a sick man is not comparable to an inoculated animal. It is not sufficient to combat the microbe, since, in this manner, post-infectious lesions would be left free to follow their evolution and the patient would succumb to autointoxication.

Although it is not safe to forecast the future, the author does not believe that serumtherapy is destined to revolutionize completely the art of healing. The method has supplied a new means of defense and success; it has enabled clinicians to reduce the death-rate and triumph where they formerly failed. The results are already sufficiently marvellous; there is no need of exaggerating them or of discrediting other methods. By the whole of reasoned procedures it is possible to overcome complex symptoms. The indications of serumtherapy should be determined, and it should be associated with other methods. Such is the path which clinicians should follow. In the meantime experimenters will perfect the methods. They will succeed in purifying the antitoxins and freeing them from useless or harmful substances accompanying them. This is the imminent discovery. When it is achieved, a new advance will have been made in serumtherapy, a new result acquired for the consolation of humanity.

CHAPTER XXIII.

THERAPEUTICS OF INFECTIOUS DISEASES (*Concluded*).

Physiological Medication. Methods Designed to Insure the Function of the Organs. Protective Rôle of the Liver. Importance of Aliments and of Cold Enemas. Medication by Ether. Protective Rôle of the Lung; Rôle of the Blood. Oxidizing Method. Rôle of the Emunctories. Sialogogues; Diuretics; Expectorants; Emetics; Purgatives. Treatment of Inflammatory Manifestations. Local Treatment. Hot Applications. Refrigeration. Immobilization and Compression. Depletion. Revulsion. Indications and Mechanism of Revulsion. Vasomotor Medication Treatment of Serous, Purulent, and Pseudomembranous Exudates, of Gangrenous and Nodular Lesions. Treatment of Hemorrhages. Chloride of Calcium. Vasoconstrictors. Astringents. Gelatin. Treatment of Fever. Cold and Hot Baths. Brand's Method. Balneotherapic Rules for Typhoid Fever, Scarlatina, Variola, Pneumonia, Bronchopneumonias, and Erysipelas. Chemical Antithermal Medicines. Blood-letting; Mode of Action and Indications. Injections of Artificial Serum: Their Action on Absorption, on Renal Elimination, on the Nervous System, and on Nutrition. Indications for Subcutaneous and Intravenous Injections of Artificial Serum. Symptomatic Medication. Treatment of Nervous, Cardiac, and Vascular Disturbances and Disorders of the Respiratory, Alimentary, and the Urinary Apparatus.

Physiological Medication.

All the forms of medication we have thus far studied were directed against the pathogenic agent. Their object was to destroy the invading microbes, hinder their development, and neutralize their toxins. The antiseptic and antitoxic medications represent the two principal methods which resume the endeavors made in this direction. Serumtherapy particularly belongs to this group. It possesses a special interest, because it constitutes a naturalistic method. By introducing a specific serum we accomplish sooner what the organism would later. Investigations in pathological physiology teach us that during infections certain organs endeavor to destroy microbes and neutralize or eject poisons. Therefore, in the study of the reactions of the organism we may find important therapeutic indications.

The efforts of the physician must tend to assure the function of the protective organs or promote their action. In all probability most of the cells of the organism play a rôle in its protection. As yet we are acquainted with but a small side of the question. We know that the liver is capable of arresting and destroying certain

microbes and toxins, and that the lungs act in the same way. We know that poisons may be eliminated through secretions, and particularly through the renal secretions and accessorily by the secretions of the digestive canal. Finally, we know that the fight against microbes and their toxins in the interior of the organism is assured by chemical modifications occurring in the plasma and by the participation of a great number of wandering cells. These changes in the fluids and cells are dependent upon increased activity of the hematopoietic organs—of the spleen, lymphatic glands, bone-marrow, and, in young children, the thymus gland.

In spite of numerous studies pursued on this subject, the facts are as yet imperfectly known. Nevertheless, certain among them may already be taken as a starting point for some therapeutic indications.

Protective Role of the Liver. Among the organs playing an important rôle in the protection of the organism against infections the liver deserves to be placed at the head of the list. Some years ago we demonstrated that this organ was capable of arresting and neutralizing a variety of poisons of external origin or formed within the diseased organism. More recent experiments enabled us to affirm that this protective action extends to toxins, at least to some of them, and to some microbes. Whether, however, the question is one of soluble products or of figurate elements, the action of the liver is not exercised unless the parenchyma contains glycogen. No matter whether this substance plays an active rôle in the phenomena of defense, or whether it represents simply an evidence of cellular activity, the only interesting point is that, to a certain extent, it enables us to measure the activity of the liver and determine with accuracy the function of the gland. Knowing the conditions under which glycogen is diminished or increased, we are able to lay down therapeutic indications calculated to maintain the protective activity of the liver.

It is often repeated that, for this purpose, it is indispensable to combat hypothermia. Fever is said to cause the disappearance of glycogen. This statement is exaggerated. When hyperthermia is engendered by inoculation of an infectious microbe glycogen remains intact during the febrile period and diminishes at the end of the infection, at the time when the temperature falls below the normal. Nevertheless, it is always advisable to combat excessive elevation of temperature as well as hypothermia. It is here that the use of baths is indicated—cold baths in the former instance, warm baths in the

latter. They re-establish the organic combustions and bring them to the rate which is favorable for glycogenesis.

The second condition which modifies glycogenesis is of still greater importance. We refer to starvation. Claude Bernard long ago demonstrated that glycogenesis is diminished in animals deprived of food. We have learned that, under the same conditions, the protective rôle of the liver against poisons and microbes is weakened. These facts demonstrate that it is indispensable to nourish infected individuals. They are no longer deprived of aliments, and are generally given milk, sometimes bouillon or other light nourishment. The author believes that warm beverages containing sugar produce, from this point of view, a very favorable effect. The sugar furnishes the most important element for glycogenesis. The patient should not, therefore, be deprived of it. It would even be better, perhaps, to utilize grape sugar instead of cane sugar. In fact, saccharose must be converted before it can serve for the formation of glycogen and the nutrition of the organism. We do not know what the activity of the inversive intestinal ferment in the course of diseases is. It would, therefore, be preferable to employ glucose. In this connection honey seems to the author clearly indicated. As is known, it contains from 65 to 75 per cent. of glucose and from 2 to 8 per cent. of cane sugar.

In recent years an endeavor has been made to increase the alimentation of patients suffering from fever. These attempts will be discussed in connection with general hygiene. It is certain, however, that from the particular point of view occupying us the method is of incontestable advantage. The importance of certain elements for the defense of the organism, notably carbohydrates, should not, however, be exaggerated. Experimental investigations pursued by us demonstrated that while small amounts of glucose increase the protective action of the liver large doses diminish it. The therapeutic amount of glucose may be said to be, at least for the rabbit, 3 grams per kilogram of animal, and 8 or 10 grams the unfavorable amount. If these results were applied to man, from 180 to 200 grams of glucose should be administered per day to an adult weighing 60 or 65 kilograms.

It is not only feeding that assures the function of the liver; therapeutics furnishes us a valuable agent—ether. As in the case of sugar, however, the effects of ether vary with the amount administered. In animals, 0.4 c.cm. of ether per kilogram of animal increases con-

siderably the action of the liver; 1 c.cm. abolishes it. Subcutaneous injection of ether produces a favorable action; but the best effects are obtained by ingestion. In this case the substance passes directly to the liver, and at the same time stimulates its glycogenic function and its action upon toxins and microbes. The application of these experimental data is very simple. When hepatic insufficiency or torpidity is suspected, 20 or 30 grams of syrup of ether containing 2 per cent. of the active substance should be prescribed per day. Stimulation of the liver may possibly be obtained by other medicines, but no accurate data are as yet at hand bearing upon this point. There is every reason, however, to suppose that purgatives and notably calomel, and perhaps certain cholagogues, exert a favorable action. More importance is attached, however, to a procedure which acts mechanically. We refer to cool enemas. Their action is double. The cold causes the vessels of the large intestine to contract and, by furnishing the liver with a greater amount of blood, stimulates its function. On the other hand, water is absorbed and brought first to the hepatic gland. As the activity of a tissue depends upon its richness in water, when fluid is furnished to an organ, it thus becomes supplied with the element which is indispensable for its activity.

To sum up, we may increase the protective rôle of the liver by feeding the patient, by prescribing substances which stimulate the activity of the glandular cells and by administering cold enemas which favor the circulation of the portal vein.

Protective Role of the Lungs. The lungs also exert considerable influence upon microbes and toxins. The conditions which may disturb their function and diminish or abolish their protective action are not well known. This much is proved, viz., that the lungs act only when oxidations take place in a regular manner. The author demonstrated this by means of artificial circulation, and Cafiero proved the same by causing a mechanical dyspnea in living animals. Inhalation of oxygen should, therefore, be prescribed when the lungs are altered and hematosis is poorly carried on. It is true, as was proved by our experimental researches, that the normal lungs act almost in the same manner, whether ordinary air or pure oxygen circulates in them. When the lungs are altered, however, such can no longer be the case, and the excess of oxygen which is brought to them must compensate for the diminution of the field of hematosis.

It is likewise possible to stimulate the action of the lungs by favoring the circulation. Cold baths are well calculated to accomplish this

end, since they diminish passive pulmonary congestion. Cupping acts in the same way. Certain cardiac medicines may also be prescribed, but most of them stimulate particularly the left ventricle, and consequently exert but little influence upon the pulmonary circulation. Under these circumstances recourse may be had to a method which has been found efficient by clinical observation in cases of pulmonary infections—that is, blood-letting.

The Role of the Blood. It is evident that other parts of the organism must likewise serve for the distribution of microbes and poisons. Our knowledge of this subject, however, is as yet limited, particularly as regards therapeutic indications of practical use. The organs and tissues as well as the fluids, and notably the blood, exercise a protective action against infectious agents. Toxins are destroyed by oxidation in the blood and probably also in the intercellular plasma. If lesions occur in the respiratory apparatus it is necessary, in order to insure the destruction of toxins, to resort to the oxidizing method. Inhalation of oxygen is then indicated. This procedure increases the amount of oxygen in the blood, and its efficiency is further demonstrated by numerous observations and experimental facts. Microbic poisons as well as those of cellular origin are thus annihilated. In this connection it is well to remember what we have repeatedly stated, namely, that oxidations are diminished in the course of infectious diseases and typhoid states. There is, therefore, every reason for intervention in all these cases. Dr. A. Robin advised the administration of benzoic acid, which increases oxidation and favors elimination of the products of disassimilation by rendering them soluble. This idea seems to us perfectly correct. We, therefore, prescribe from 2 to 4 grams of benzoate of soda daily in grave infectious states, notably when the lesions of the liver, lungs, or kidneys seem to hinder the evolution or elimination of the toxic products originating from disassimilation. If the liver is at the same time disturbed we prescribe in the same potion with 70 grams of julep, 4 grams of benzoate of soda and 30 grams of syrup of ether; a tablespoonful is taken every hour. Although oxidation is a general procedure of attenuation of toxins, a by no means less important rôle is played by the cells which are capable of picking up and digesting microbes and secreting substances which diminish their activity and neutralize their toxins. The therapeutist must, therefore, endeavor to stimulate phagocytosis and favor germicidal and antitoxic secretions. Unfortunately, we possess but little information on this sub-

ject. All we know is that injections of artificial serum give rise to an abundant proliferation of the cells of the bone-marrow. The latter tissue furnishes the economy with the greatest part of the leucocytes charged with the function of defense. Hence it is not difficult to understand the excellent effects of these therapeutics in all cases in which the reactions of the organism seem to be insufficient.

Role of the Emunctories. After undergoing in the organism a series of transformations, the toxic substances are eliminated through the various emunctories. Some of them pass into the stomach; others, notably the poisons of the colon bacillus, are thrown into the intestine. Their elimination may, therefore, be hastened by lavage of the alimentary canal. The kidneys, however, are the principal route of elimination. It must be remembered that in the course of infections the urinary secretion is diminished, and in general the toxicity of the urine is also lessened. The physician must endeavor to favor diuresis. For this purpose the patients must be given plenty of water, also enemas which they may retain, at least in part. When necessary, salt-water may also be injected beneath the skin. A second indication is drawn from the state of the blood pressure. With the assistance of Dr. Garnier, the author has found in several cases of scarlatina that when the urinary secretion is very scant, and especially when temporarily suppressed, the blood pressure rises; the heart, by the energy of its contractions, seems to strive to overcome the renal barrier. On the basis of this fact, the physician must endeavor to still raise the blood pressure. Certain medicines may accomplish this end. It is better, however, to resort to cold baths. In patients constantly treated by baths the renal secretion becomes profuse, and, as is demonstrated by the study of urinary toxicity, it carries off noxious substances. The elimination thus being carried on during the entire course of the disease, the mode of its termination is often modified. Such is notably the case in pneumonia in which the urinary crisis, which is no longer any *raison d'être*, is not produced. Another cause disturbing diuresis is the fact that the excrementitious substances are not sufficiently oxidized. In this connection, cold baths exercise a favorable action which, as already stated, may be completed by the administration of sodium benzoate. This medicine is likewise to be resorted to when lesions of the kidneys hinder the function of these organs. It would then be useless to prescribe diuretics, which would only increase the lesions by stimulating the cells which are already diseased.

When infectious nephritis is too intense or extensive, it will be necessary to diminish intoxication by stimulating elimination through other channels, notably by the digestive tract and, in grave cases, by blood-letting. The author does not trust much in the vicarious rôle of sweating. Nevertheless, in certain diseases, the sweat seems to throw out toxic substances. In several cases of diphtheria treated by subcutaneous injections of pilocarpine we noticed, in consequence of sweating, very great amelioration in the general state. It would, therefore, be worth while to take up this study and to learn whether the old therapeutics, which treated fever patients by giving them hot drinks, diaphoretics, and by covering them heavily, did in certain cases yield good results through the sweating thus produced.

The secretions of the organism at times eliminate morbid productions resulting from microbic action or a reaction of the economy. Thus, the pseudomembranes of diphtheria localize infection and oppose penetration of the microbe and its toxins into the economy. The organism has done well in producing these pseudomembranes, but it will be equally advantageous for it to eliminate them at a certain period of evolution. Hence, it strives to detach them by means of a secretion of the subjacent glands and by increased activity of the salivary glands. It is easy to stimulate this process by administering sialagogues and notably pilocarpine. The action of this medicine upon the heart is much dreaded. It must, therefore, be employed with caution. In adults, however, the author has obtained excellent results from its employment in the treatment of pseudomembranous anginas and particularly diphtheritic sore throat. He prescribes a subcutaneous injection, morning and evening, of 10 drops of a 1 per cent. solution of nitrate of pilocarpine. In twenty-four or forty-eight hours the pseudomembranes are detached and the patient experiences a very notable improvement in his general state.

Sialagogues may also be employed in all sorts of buccal infections. The one most frequently used is chlorate of potash, which is administered in daily doses of from 2 to 4 grams. The action of this medicine is admittedly due to its passage into the saliva. The amount eliminated through this channel, however, is quite small; it amounts to hardly 3 per cent. It is to be recognized, however, that in this case the local treatment has more influence than the salivary excitation.

Medication is also physiological when the elimination undertaken by the organism is stimulated by the employment of the same pro-

cedures utilized by the economy itself. Bronchial and pulmonary lesions result in expectoration calculated to throw out the exudates, the signification of which is exactly the same as that of pseudomembranes in diphtheria. Physiological medication consists in prescribing expectorants. These are divided into two groups, according as they act by increasing the force with which the bronchi throw out their contents or by modifying the exudate of the respiratory apparatus. Emetics act mechanically. A second group contains expectorants. The most important expectorants are those which liquefy the exudates. The first among them is chlorohydrate of ammonia, an excellent medicine, which is to be given to children in half-gram doses daily, and from 2 to 4 grams to adults. It may be combined with the salts of antimony. White oxide of antimony seems to the author by far the better preparation, provided it is not employed in too strong doses. The author has obtained excellent results by giving 20 cg. to 30 cg. a day. It is an insoluble salt which may be given in water. If emetics are given in small doses so as to avoid vomiting and nausea, they act as expectorants. Ipecacuanha may thus be prescribed in fractional doses: apomorphine, 1 mg. every hour in the form of pills or in a potion. For example, one may prescribe as follows:

Crystallized hydrochlorate of apomorphine .	0.01	centigram ($\frac{1}{6}$ grain).
Hydrochlorate of morphine	0.03	" ($\frac{1}{2}$ grain).
Hydrochloric acid	3	drops.
Simple syrup	30	grams (℥j).
Water	90	" (℥iij).

Lastly, the syrup of polygala seems to belong to this group, but it should not be employed if there is fever or digestive disorders.

Physiological medication is applicable to a great number of gastro-intestinal disorders. When the gastric disturbances give rise to nausea, an emetic is called for in order to achieve the work begun by nature by ejecting the substances which encumber and hurt the gastric cavity. Likewise, in patients suffering from diarrhea, which expresses a natural therapeutic tendency, excellent results are often obtained by prescribing a purgative. On the other hand, in certain cases it is advisable to increase constipation; in peritonitis and in intestinal hemorrhage the movements of the bowels may intensify the disorders. It is, therefore, desirable to immobilize the digestive tract. For this purpose opium is mostly prescribed in the form of the extract, 1 cg. every hour.

In brief, such are the various medicines which may be employed when we wish to practise physiological medication. All of them increase certain morbid manifestations, or, more exactly, they favor the reactions which the organism calls into play in order to combat microbes and their toxins.

Reactions are not always of the desirable kind, however. In a great many cases they may give rise to new derangements by their intensity and persistence. They must then be combated. This would be contra-physiological medication, the indications and procedures of which will be discussed in connection with symptomatic therapeutics.

Treatment of Inflammatory Manifestations.

If it were possible in every case to attack the cause of the disturbances, the treatment of inflammatory manifestations would always draw its indications from etiology. Antiseptic medication, when applicable, responds to this indication. When the cause cannot be reached, and it is impossible to act upon the mechanism which engenders the morbid phenomena, it is necessary to resort to physiological medication. In all cases of inflammation two series of phenomena are to be taken into account: those which occur at the diseased spot and require local treatment, and those which result from disturbances engendered by the primary lesion in other parts of the organism and require general treatment.

Local Treatment. Local treatment may be directed either to moderate or, on the contrary, to stimulate and increase inflammatory manifestations. In the former case the method is called antiphlogistic. Now, if we take up the four cardinal phenomena of inflammation, we shall see that each of them may quite readily be combated or stimulated.

Hot Applications. Let us first consider heat. Increase in local temperature indicates increased activity in nutritive exchanges, which augments the production of heat. At the same time, as may readily be noticed by applying the hand to the diseased spot, there is increased dissipation of heat. Exaggeration of metabolism brings about a more marked vascularization, whence the second phenomenon, redness.

In the presence of these two symptoms the therapeutist may think it advisable to stimulate inflammation. He resorts to hot applications. He thus acts upon the production of heat and, it seems, he

practises naturalistic therapeutics. It is to be noted, however, that by this local treatment he imperfectly imitates nature, for it hinders the second phenomenon—*i. e.*, increased radiation. If, for example, the diseased part be immersed in very hot water, or if hot compresses be applied, the temperature is evidently increased, but radiation diminishes. Nevertheless, this method yields good results. It is utilized especially in cutaneous inflammations. In the treatment of erysipelas the author applies upon the affected parts compresses of gauze dipped either in hot water or some weak infusion. Such compresses should not be allowed to become cold, for the evaporation of the water dissipates the heat and produces a contrary result. Hot poultices have the advantage of better preserving heat, and may be prescribed under the same circumstances. In order to avoid the inconvenience resulting from evaporation or moisture, the diseased part may be surrounded with rubber tubes in which hot water is circulated. It is likewise possible, in the case of the abdomen, to place upon the part rubber bags filled with hot water. When treating the extremities one may employ for the same purpose small bags filled with sand, which may be placed under and around the limbs, while the upper surface may be covered with a bag of hot oatmeal in order to avoid too much weight. Lastly, when the lesion is well circumscribed, hot air may be employed, as, for example, in the case of soft chancre.

Refrigeration. Refrigeration may be accomplished by application of cold compresses or poultices, by circulation of cold water in tubes, by cold air and application of bags filled with water or ice. When an ice-bag is employed a flannel should be interposed between the bag and the skin in order not to hurt the skin. This method evidently increases radiation and diminishes heat; on the other hand, it gives rise to vasoconstriction, which causes the second cardinal phenomenon—*i. e.*, heat—to disappear. This method is hardly ever applicable to superficial lesions. Inflammations of the skin, of subcutaneous tissue, and of lymphatic glands should not, as a rule, be treated by means of refrigeration. These inflammations already have a certain tendency to sphacelation, which would be increased by cold. Brown-Séquard believed that cold and hot applications should be used alternately; the reverse modifications which are thus produced in the vessels hinder the production of gangrene. The author believes that heat is sufficient for this purpose.

The refrigerating method, on the contrary, renders immense service

in the treatment of deep inflammations. In acute inflammations of the abdominal organs, in appendicitis, peritonitis, and periuterine lesions remarkable results are obtained. Likewise, the application of an ice-bag upon the precordial region or upon the cranium is classical in cases of inflammation of the pericardium or meninges, respectively. The author employs the same method when, in the course of otitis, he finds symptoms of mastoiditis. The application of the ice-bag upon the mastoid region succeeded, in several cases, in arresting the accidents. It must be borne in mind, however, that care should be taken not to allow the bag to grow warm. When the ice-bag is used it must be renewed from time to time.

Cold may likewise be employed to assuage the third cardinal phenomenon—pain. It produces very marked sedation and acts upon the pain of mastoiditis or osteomyelitis as well as upon that of orchitis. The action of cold is complex. Besides the waste of heat, cold causes constriction of the bloodvessels. Not only the small arteries of the skin but also those of the deeper parts become constricted. The experiments of Fredericq leave no doubt in this regard. The application of the ice-bag upon the cranium produces constriction in the cutaneous and meningeal arteries. The latter are too rapidly reached to permit the supposition that the phenomenon is due to the propagation of cold; it is probably a process of reflex vasoconstriction.

Moreover, cold increases the tonicity of the vascular muscles as well as those of the myocardium. The latter result has considerable importance. Application of the ice-bag over the region of the heart may be prescribed in all cases of myocarditis whenever it is necessary to render the function of the organ more regular and energetic.

Immobilization. Every inflammatory lesion causes pain and swelling which disturb considerably the function of the affected parts. The patient instinctively immobilizes himself as much as possible. Rest of the inflamed parts is one of the best therapeutic measures. It is constantly resorted to in surgery. The application of splints and apparatus is designed to prevent every movement of the inflamed parts, and thus complete the natural work. In certain cases it is possible to arrest the inflammatory swelling by means of a methodic compression; but this latter method is hardly ever indicated in cases of acute inflammation. The results obtained by submitting inflamed parts, and notably the skin affected by erysipelas, to the elastic compression of a layer of collodion have not been encouraging.

Compression may be useful by hastening the absorption of exudates only after the acute phenomena have passed away.

Depletion. Inflammatory congestions and exudations are often combated by depletion. Scarifications upon the diseased parts are useful, as they permit the discharge of a small amount of blood or serosity, thus relieving considerably the painful tension of which the patient complains. Some have even attempted to arrest the progress of certain inflammations in this manner. Thus, scarifications have sometimes been practised upon an erysipelatous patch. The procedure does not seem, however, to have given satisfactory results.

Revulsion. Revulsion is often practised upon the region of the skin corresponding to the diseased organ as well as in distant parts. Dry or scarified cupping of the precordial region and sometimes application of leeches are often prescribed in cases of acute inflammation of the cardiac muscle and especially of the serous membranes. The same means are applied in the treatment of pleuropulmonary and abdominal inflammations; or, instead of these mechanical procedures irritating substances, such as mustard poultices, friction with croton oil, and application of certain plasters may be prescribed. In other cases applications are made to distant parts. In cases of thoracic or cerebral inflammation revulsion is effected by cupping the extremities, applying leeches to the anus or mustard plasters upon the legs. In the conception of the ancient practitioners, all these medications had the same object. They were intended to draw the inflammation of the diseased organ toward those parts of the organism where it would cause no harm. Such was the idea of Hippocrates, who practised revulsion, and in this manner proposed to draw away the humors which threatened to attack an important organ. Most modern therapeutists, instead of the humoral hypothesis of revulsion, hold the nervous theory to be true. They admit that excitation at one point causes, by means of inhibitory acts, palliation of congestive and inflammatory phenomena occurring in another part of the economy. The revulsive application calls into play the sensory system, and coincidently it produces a series of circulatory modifications.

Among the revulsives, some, like sinapisms, cause congestion in the skin, and thus modify the water content of the blood. Others produce extravasation of a quantity of blood; such is the case in dry cupping. Still others produce local blood-letting. In the last-named case, between the superficial and the profound circulation a balancing is admitted. The effect is deeper, however, and the flow of blood

may relieve the venous system. To this end blood-letting should be practised at a determined point. Thus, in order to diminish passive congestion of the brain, leeches must be applied upon the mastoid processes. When action upon the liver is desired, they are placed about the anus or even upon the anal mucous membrane. Hepatic depletion is explained by the vascular connections which unite this region to the portal system.

In brief, revulsion seems to act in two ways: by producing depletion of blood and a reflex excitation, expressed by an inhibitory action upon the inflamed part. It is probably owing to nervous connections between the superficial and deeper parts of a region that revulsion is effected, preferably in the part corresponding to the diseased organ. This mode of excitation belongs to all revulsives, because all produce excitation of the nerve terminations. Some of them also give rise to circulatory modifications by inducing congestion, ecchymoses, or depletion. In the latter case a general modification in the blood is produced in addition to the local change. The remarkable effects of local depletion are not, however, to be attributed to the latter result. All scarified cuppings applied to the precordial region do not act like general blood-letting. It is, therefore, probable that there is a harmony in the vascular or vasomotor system of the same segments of the body. A modification produced in the local circulation of one part of the segment must affect preferably and in a special manner the subjacent parts. Whatever be the theory, the practical importance of revulsion is undeniable. It is resorted to in two cases, namely, at the beginning of inflammation and at its terminal period.

At the beginning the immediate result of revulsion is frequently to assuage one of the elements of inflammation to which we have thus far hardly referred, viz., pain. The pain in the side felt in pneumonia rapidly yields to a few dry cuppings and still more readily to scarified cuppings. The same is true of the painful distress of patients suffering from acute pericarditis. At the same time the congestive phenomena are rapidly palliated and, consequently, the inflammation is relieved. It may be objected that inflammatory reaction is of secondary importance and that there is no advantage in combating it. This remark would be perfectly exact if the organism always proportioned its efforts to its needs. As we have time and time again remarked, however, slight causes often produce extremely violent reactions. We may recall, for example, a benign cutaneous lesion,

such as furuncle. Around the small lesion, which must arrest and destroy the staphylococcus, an edema develops which sometimes assumes enormous proportions. When the seat of the phenomenon is the skin no great harm results; but if the process occurs in a vital organ like the heart, the diffusion of the lesion may have fearful consequences. Hence, revulsion is necessary, and it is the more useful as the affected part occupies a higher rank in the organic hierarchy.

Revulsion is likewise employed at the end of the morbid evolution when recovery is tedious. In this case depletive measures are not resorted to; but excitants, such as sinapisms, vesicatories, and thermal cauterizations are applied. By excitation of the nerve ends we bring about increased nutritive activity of the parts which are operated upon and those which are subjacent.

We thus arrive at the conclusion that revulsion is not comprehensible unless we admit a nervovascular synergy establishing a morbid sympathy in the various segments of the body. According to this view, it is intelligible why revulsion practised upon the spinal column influences the viscera. While certain parts possess a relative autonomy, all are united by numerous synergies. Hence, it is conceivable that a local modification may produce extensive effects. It is for this reason that we may act upon a thoracic organ by applying revulsives to the lower extremities.

In the beginning of all local inflammations local revulsion must be practised. The choice of the revulsive varies with the age and state of the individual. In young children we have often to treat pleuropulmonary inflammations. We must resort to mustard poultices and baths, and envelop the patient with moist sheets. It is to be borne in mind that blood-letting, even of a local character, is not, as a rule, well borne by children. In the case of vigorous adults, scarified cupping represents the best method of taking blood. In debilitated subjects and delicate women milder revulsives, such as dry cupping, sinapisms, must generally be resorted to and, in graver cases, thermocauterization. Intervention must be more energetic the more important or delicate the affected part. Cardiac and cerebromeningeal manifestations thus require the promptest intervention.

When chronic lesions are to be dealt with, thermocauterization, vesicatories, and at times simply application of tincture of iodine, are employed. An abscess (*l'abcès par fixation*) produced by means of a subcutaneous injection of turpentine is a method related to the group of revulsive procedures. Its mode of action has been discussed.

Some authorities contend that the circulating bacteria are attracted to the abscess, others admit a modification produced in the phagocytes and hematopoietic organs. This method, first employed in puerperal fever, then in various septicemias, has been utilized with success in the treatment of grave pneumonias.

Vasomotor and Depletive Medications.

We have thus far reviewed the methods which act locally upon inflamed parts. There are, however, other modes of treatment which modify the general state. The therapeutist may have two objects in view: to stimulate or attenuate inflammatory manifestations. In the former instance he employs vasodilators, and administers, for example, trinitrin, or causes the patient to inhale nitrite of amyl. We often resort to the first of these medicines in the treatment of erysipelas. In certain cases characterized by a tedious course and lingering resolution, truly interesting results are obtained. Inhalation of amyl nitrite has been employed by Dr. Hayem in the treatment of pneumonia.

On the other hand, when it is desired to check the inflammatory phenomena, ergotin or tartar emetic is sometimes prescribed according to the method of Rasori. The latter medicine is employed especially in pneumonia. When the individual is vigorous and the congestion is extreme, from 10 cg. to 20 cg. of it is prescribed in a potion of 120 grams ($1\frac{1}{2}$ grains to 3 grains in 4 ounces); a tablespoonful is given every two hours.

Another method consists in combating inflammation by means of general depletion. Two procedures are at our disposal: we may give rise to a serous exudation, and for this purpose, purgatives and drastics are prescribed. This medication is alike evacuative and revulsive, as it not only causes depletion but intestinal irritation as well. All inflammations do not require this method. It is indicated particularly in meningeal and cerebral inflammations. Calomel is preferably employed. In adults this substance is administered in doses of from $\frac{1}{2}$ gram to 1 gram (8 to 15 grains) divided into three powders and given at intervals of fifteen minutes. In children from 10 cg. to 30 cg. ($1\frac{1}{2}$ to 5 grains) are prescribed; 15 or 20 grams (half an ounce) of castor oil is given the following day. This is the classical practice in England, and is to be recommended. A last therapeutic means consists in producing depletion by blood-letting. In view of the importance of this method, we shall devote to it a special chapter.

Having studied inflammation and its treatment in a general manner, it now remains to consider the therapeutics of its various consequences. We shall begin with the study of exudates.

Treatment of Inflammatory Exudates.

Treatment of Serous Exudates. When inflammatory exudates acquire a certain volume or occupy an important organ or tissue, they require treatment varying according to their seat and nature. Their nature may be serous, pseudomembranous, purulent, or putrid.

The serous exudates exert upon the pathogenic microbes a germicidal influence and, consequently, represent a salutary reaction. It will suffice, for example, to recall variola. In its confluent forms the edematous swelling of the face and hands constitutes an excellent sign of prognosis. In certain cases, however, the effusion takes place in an important organ or a delicate tissue. It may then have two inconveniences: at times, owing to its large volume, it acts mechanically and hinders the regular function of the organ. At other times it separates superficial parts from deeper layers, and thus embarrasses their circulation and nutrition, and may even cause their mortification. In a more advanced degree the exudate, instead of being simply diffuse, predominates at one point. It may then raise the skin or the mucous membrane, producing bullæ or phlyctenulæ. This is what occurs in the most varied affections, such as herpes, varicella, erysipelas, pemphigus, etc. When a serous cavity is adjacent to the inflamed part the fluid naturally flows into it. Pleurisies, peritonites, pericardites, meningites, vaginites, and arthrites which are the equivalents of edemas and bullæ, are thus produced. The disposition of the tissues being more favorable for the free flow of the fluids, the latter exude in greater profusion.

The effusion taking place in a serous membrane likewise represents a germicidal exudate. Its relations to the subjacent organs, however, produce a certain number of functional disturbances and suggest some interesting therapeutic indications. Thus a pleurisy, on account of its abundance, may embarrass pulmonary hematosis and give rise to progressive asphyxia, and even cause sudden death. In face of these dangers the question is whether the exudate is to be respected on account of its advantages. By compressing the lungs and restricting their expansion, by hindering their function, the effusion checks their activity and condemns these organs to a state of relative rest, or it brings about immobilization recalling that which

the physician practises upon a diseased joint. The problem thus becomes highly complex. It would be equally rational to argue that the effusion, by restricting pulmonary activity, hinders hematosis, and consequently disturbs the entire organism. On the other hand, it may be contended that the effusion necessitates a relative rest on the part of the diseased lung, and thus favors cicatrization of the lesion. The interest of this discussion is not merely one of speculation; on the contrary, it guides therapeutics. If the bad effects are thought to overbalance the advantages, early intervention is necessary to evacuate the fluid by thoracentesis. On the other hand, the physician should not intervene unless the effusion, owing to its great abundance, threatens to produce grave disorders. Even then, however, evacuation of only a small amount of the exudate will suffice, because complete evacuation is often followed by a too energetic flux of the blood into the previously compressed vessels, and a consequent intense congestion. It is, therefore, almost universally agreed that the operation should not be performed during the acute stage. The intervention is to take place after the effusion has become stationary. If the fluid tends to be absorbed then nothing is to be done. On the contrary, if it persists without any notable modification, intervention is indicated. If the fluid is allowed to remain too long, atrophy of the lungs, thickenings, and adhesions may occur, which embarrass the function of the organs and bring about deformity of the thorax. Thoracentesis is practised generally toward the fifteenth day in children and the twentieth day in adults. All the fluid is not drawn, however; at most one quart (one litre) should be evacuated. If the fluid is reproduced a new puncture may be made. In most cases, however, after the first evacuation absorption is completed of itself. This fact is not to be wondered at. It is the application to serous membranes of the general law of pathology. Every microbic lesion at the end of a certain time no longer tends to arouse organic reactions. The economy becomes accustomed to the presence of an infectious focus which at first arouses its susceptibility. A *modus vivendi* which may be prolonged almost indefinitely is thus established. Intervention is then indicated. The organism being sluggish, the operation renews the inflammatory process and produces an increased circulatory activity in the lungs, and the change thus caused is eminently favorable to the absorption of the exudate.

There is another question to which hardly an allusion has thus far been made. Do exudates in general or, what is easier to study,

pleural effusions contain figurate elements or soluble substances exerting any action whatever upon the organism, either favorable or otherwise? At present it is well known that even serous and transparent effusions always contain leucocytes. What is the significance of their presence from the standpoint of the protection of the organism? Of this we know nothing, and we do not comprehend their rôle in those cases in which the exudate is germless. On the other hand, as has already been stated, even a serous effusion may contain bacteria, notably streptococci. In the case of tuberculosis, it often contains the specific bacillus, as has been demonstrated by inoculations into animals. This presence of microbes in certain exudates might, perhaps, justify and command earlier intervention. The author says "perhaps," because, besides the difficulty encountered in determining whether living bacteria are present in an exudate or not, it may furthermore be questioned whether these bacteria are really noxious. Immersed as they are in a great amount of germicidal fluid, they seem to have lost all pathogenic action, since they are incapable of inducing even a purulent transformation of the exudate. Investigations should be pursued on this subject. It would also be interesting to take up the study of soluble toxic or antitoxic substances which may be present in an exudate. Dr. Gilbert (of Geneva) laid down the problem by showing that the fluid of tubercular pleurisies, when injected beneath the skin, exerts a curative action. It is true that the fact has been doubted. The author has therefore, with Dr. Josué, pursued some researches with the fluid of experimental diphtheritic pleurisies. The results were negative, inasmuch as the fluid experimentally produced in guinea-pigs contained neither toxin nor antitoxin.

We have expanded upon pleural effusions, for they are the most frequent, while exudates in other serous membranes are of quite uncommon occurrence. While, in the case of pleurisies the physician must be guided in his intervention by the physical signs and the course of evolution, and not by the functional disturbances which are extremely deceiving, in the case of pericardial or meningeal effusions he must act altogether differently. In the case of the pericardium the physician must intervene when the effusion endangers the function of the heart, and in the case of the meninges, when the exudate produces compression and intense headache. Lumbar puncture relieves the pain and temporarily reduces the increased intrameningeal tension as well as certain alarming phenomena,

notably coma. In most cases amelioration is transitory and only delays the fatal termination. Nevertheless, there are certain cases on record in which repeated punctures seem to have contributed to recovery. At any rate, this inoffensive operation seems destined to be retained in medical practice as a palliative.

Acute inflammations of the peritoneum, unlike those of the pleura, seldom result in a serous effusion which, in case it should be produced, is too small in amount to necessitate operative intervention. In fact, there is a production of pseudomembranous exudates which embarrass intestinal movements. This is a fortunate event, since the extension of the peritoneal inflammation is nothing else than a series of inoculations which take place from point to point as a result of contractions of the intestine. It is well, therefore, to complete the work of nature by further immobilizing the intestinal coils, a result that may be obtained by the administration of opium or morphine. Operative intervention is at times indicated only in subacute or chronic infections, and notably in tuberculosis. Two kinds of operations may be performed: one simply palliative, the other curative. In the so-called ascitic form of tubercular peritonitis paracentesis is practised because the effusion, owing to its abundance, produces functional disorders. The liquid, however, is seldom sufficiently profuse to render this operation necessary, and, on the other hand, it is generally contained between adhesive bands of pseudomembranes which prevent its free flow. It is true that the operation may be completed by irrigating the serous membrane by means of boiled borated water at 102.2° or 104° F. (39° or 40° C.). Irrigation is continued until the returning fluid becomes perfectly clear. This method, for which we are indebted to Dr. Debove, has been employed with success in a number of cases. The irrigations are followed by a sufficiently strong inflammatory reaction. The lesions subsequently undergo resolution. Another procedure, the efficacy of which was demonstrated by the experiments of Dr. Teissier, consists in injecting into the peritoneum sterilized gases—oxygen or nitrogen.

Lastly, one of the most extraordinary therapeutic methods applied to tubercular peritonitis is laparotomy. The peritoneal cavity is opened, and then, after irrigation by means of boiled water, it is dressed. As a result the lesions subside. In this manner recovery has been obtained in 75 per cent. of the cases in adults and 87 per cent. in children. This is what takes place, at least in the ascitic form. In the ulcerative variety, out of twenty-two laparotomies nine

were followed by death. Out of thirteen other patients, only three remained in a satisfactory state. Finally, in the fibrous variety, recovery reaches 65 per cent. The mechanism of recovery following operative intervention has been a subject of extensive discussion. Numerous experiments have been undertaken bearing upon this subject. All clinical as well as experimental documents show that laparotomy succeeds particularly in those cases which tend toward recovery or at least toward a chronic state compatible with life. The slightest cause is then sufficient to arouse the sluggish reactions of the organism. Laparotomy, still better than aseptic irrigations or injections of gas, produces a slight inflammation and, necessitating an effort of reparation on the part of the organism, brings about cicatrization of both the operative wound and the pre-existing lesions. The organism, being forced to supply cells and to secrete exudates for the reparation of the surgical incision, resumes coincidently the work which it had once begun for the destruction of the tubercle and of the infectious agents living therein. In brief, all these therapeutic procedures act simply by awakening a curative inflammation which had too soon fallen into slumber.

Serous effusions of the tunica vaginalis or of the articular synovials seldom invite operative intervention. In cases in which the pain caused by inflammation of the tunica vaginalis is very intense, a puncture is practised which, diminishing the tension, causes the painful phenomena to disappear. Finally, as in the case of the pleura, when the effusions pass into a chronic state and present no tendency to absorption, the fluid must be evacuated. As in the case of the pleura, however, it seems that effusions of the serous membranes are always produced consecutively to a lesion of the neighboring parts, and especially of subjacent organs. Hydrocele is a true chronic inflammation of the tunica vaginalis. It is to be noted that, unlike what occurs in other serous membranes, evacuation of the fluid does not suffice to bring about recovery. It is necessary, in addition, to inject an irritant and give rise to a curative inflammation.

In those cases in which the serous exudates raise the epidermis or the epithelial lining of a mucous membrane which is readily accessible immediate intervention is evidently indicated. The bulla should be punctured by means of a sterilized needle, and the fluid evacuated by gentle pressure with the finger. The operation is done precisely as in the dressing after the application of a vesicatory. By this small operation the painful tension is diminished and the liquid

containing microbes and toxins is thrown out. Finally, repair is favored because, without this precaution, suppuration or ulceration might take place.

When serous exudates are produced in visceral cavities and notably in the digestive tract, an easy issue is assured. The organism daily employs this means of defense. Vomiting and diarrhea represent the production of serous secretions designed to combat infection, viz., to eliminate microbes and their toxins. Therapeutics is guided by the same principles in prescribing emetics and purgatives. These medicines produce secretions which wash the affected parts. An emetic may likewise serve to eject exudates produced in the respiratory apparatus. The movements of the diaphragm and the thoracic muscles compress the lungs and expel the pathological fluids encumbering them.

Treatment of Purulent Exudates. While serous exudates are dangerous only by their quantity and the disturbances which they mechanically cause in the neighboring organs, purulent exudates are of greater importance and require more prompt intervention.

Purulent transformation is indicative of great activity on the part of the pathogenic agents. Their toxins give rise to profuse diapedesis. While the leucocytes are not killed in the yellow serous exudate, in pus they undergo a special transformation—a fermentation —which causes their death and changes them into useless foreign bodies. As has already been stated, a serous effusion produces nothing more than mechanical disturbances. A purulent effusion, on the other hand, modifies the organism more profoundly. The general state is affected, fever sets in, and grave phenomena may appear. This different mode of action of the two kinds of effusions results in profound difference in the reactions of the organism. When effusion is of a serous character, the organism makes no effort to throw it out; when effusion is purulent, modifications which terminate in the evacuation of the morbid focus occur. This is the tendency of every purulent focus, viz., to open outward or into a cavity. These spontaneous openings, however, have three inconveniences: they may occur in an organ of great physiological importance or enter a cavity which may serve as an excellent medium for the multiplication of the microbe. The result is often the occurrence of serious accidents rapidly ending in death. A visceral abscess, until then well borne, when it discharges into the peritoneal cavity, produces inflammation in the serous membrane which ends fatally. In this case the organ-

ism follows its tendency to throw out the harmful element, but its intervention is blind and gives rise to graver disorders than the primary lesion.

The second inconvenience of spontaneous openings, even of those which occur under favorable conditions, is that they are effected too tardily. The consequence is that the organism is subjected too long to the action of toxins and that the adjoining parts of the purulent focus are too profoundly altered to recover. Finally, the spontaneous openings are generally too small, the discharge is not well effected, and the pus stagnates and may undergo putrid decomposition. Or else fistulous tracts are produced, ending in the formation of permanent fistulæ. If suppuration is finally arrested, deformed cicatrices persist which often cause functional difficulties. These considerations explain why timely intervention is necessary. Incision permits the flow of the pus under the most favorable conditions at the most favorable point, through a sufficiently large opening and at a period when the economy is not too profoundly intoxicated and when the neighboring parts of the focus are not yet deeply affected. Incision must be practised as soon as the pus is collected, and it must be made at a low point. If the focus is large and presents ventricles, it is often necessary to make counteropenings. In order to assure the flow of the fluid and prevent the incision from closing prematurely, the lips of the wound should be kept open by means of gauze or drainage-tubes. When dealing with a voluminous but well-circumscribed abscess, situated in the face or neck, the author has been in the habit of making a small puncture and introducing into the focus Florence horsehair curved in arch-shape in order to avoid a cicatrix. In this way a very easy discharge is assured, and the incision is so small as, in most cases, to leave no visible mark.

In all cases the discharge should continue for a few days following the incision. The exudate then represents a sort of washing performed by the organism for eliminating the microbes and toxins. Guided by this fact, lavage with aseptic or slightly antiseptic fluids may be employed, and the work of nature thus be completed. These lavages also have the advantage of detaching and washing out dead cells, small foreign bodies, and at times sequestræ. Spontaneous rejection of these harmful elements is long and difficult. Even lavage may be insufficient to carry them away. Then curettage and, in certain cases, more important operations are resorted to for the purpose of exposing necrosed parts and extracting them. An osseous

sequestrum, for example, may keep up a discharge for years, but when it is extirpated, recovery follows in a few days.

Medical advance, by enabling the practitioner to detect visceral suppurations and establish their localization by the study of symptoms, have led him to intervene in cases of deep-seated lesions, visceral abscesses, such as those of the liver, kidneys, and lungs, or of the nervous centres, and to open serous cavities, and to trepan a bone. Surgical intervention is not, however, always indispensable. Purulent foci are sometimes suppressed spontaneously, and the microbes perish. The pus is then absorbed or undergoes fatty metamorphoses, or else it is transformed into a semisolid mass which may later become infiltrated with calcareous salts, and thus be rendered entirely inoffensive. In order to formulate the rules of intervention, we must take into account a good many factors, such as the seat of the lesion, the nature of the causative microbe, the course of the local symptoms, and the concomitant general phenomena. As regards localization, it will suffice to recall what occurs in the serous cavities. Intervention must be immediate in the case of the peritoneum, in order to prevent an early fatal termination, and it must be prompt in the case of articulations, in order to prevent consecutive ankylosis. On the other hand, purulent pleurisy is far better borne, and at times, when it is encysted, it may heal spontaneously by vomica. Early intervention is, however, preferable, since it prevents secondary alterations of the lungs and pleura. The nature of the causative agent is also to be considered. As a rule, suppurations with streptococci require rapid intervention and radical operation. A large incision, assuring an easy flow, is indispensable. Suppurations due to pneumococci are less liable to be reproduced and often recover in consequence of simple evacuative puncture. Finally, non-microbic suppurations are commonly well borne and may be absorbed without operative intervention.

Besides bacteriological examination, which alone can conclusively demonstrate the nature of the causative agent, therapeutic indications may be drawn from the local and general phenomena. Thus the author has seen the development of a pleuritic effusion during convalescence from typhoid fever. This effusion, occurring without any functional disturbance and giving rise to no fever, seemed to be of a serous nature. In order to assure the diagnosis, however, a few days later the author made an exploratory puncture, which brought out a seropurulent liquid. The latter, however, contained no microbe,

but agglutinated energetically the typhoid bacillus. As the general state seemed to be very satisfactory, he did no more than apply a few cutaneous revulsives, and the fluid was gradually absorbed and disappeared. Here is a case in which the study of the morbid symptoms did not justify intervention; but in the case of an erroneous interpretation of the nature of the effusion, exploratory puncture, by giving exact information, might have modified our first conclusion. Bacteriological examination, however, brought us back to the idea of abstention, and the evolution demonstrated that in fact it was useless to intervene.

We cannot review all the indications and contraindications that are to be taken into account when the rules of intervention are to be settled. While in certain cases these rules are relatively simple, in others discussion is not yet at an end. It will suffice to recall what occurs as regards appendicitis. The lesion is not treated by incision of the focus, but by extirpation of the diseased organ. While certain surgeons operate as soon as the diagnosis is made, others prefer to wait and not intervene until after the disappearance of the acute symptoms. In view of the discussions that have taken place and of the contradictory facts that have been reported, it may be stated that at the present time no problem is more troublesome, no question engages more responsibility or produces more anxiety than the advice to be given in cases of appendicitis.

Although surgical intervention is possible when suppuration is localized at a point, it cannot evidently be resorted to against small disseminated lesions. We may open a pulmonary abscess, but we are unable to intervene against a purulent bronchitis or a bronchopneumonia which has terminated in multiple lobular suppurations. In this case the organism endeavors to eject the purulent exudates by coughing and at times by vomiting. The physician must act in the same manner. He must prescribe substances which favor liquefaction of the exudate and, consecutively, its ejection through expectoration. The sulphur and antimony preparations are indicated here. If this medication proves insufficient, an emetic may accomplish more thorough cleansing of the respiratory apparatus. While, however, an emetic yields good results in young children, the older the patient the less easily he can bear it. It should never be employed in the aged, since it may, by the efforts which it produces, cause vascular ruptures or, at least, give rise to considerable depression and collapse.

Treatment of Pseudomembranous Exudates. The third variety of inflammatory exudates is represented by pseudomembranous exudates. The therapeutic rule is here very simple. The false membrane is a barrier opposed to the infection, but it is full of microbes and toxins. The organism should, therefore, be freed from it. This may be accomplished by irrigations, scrapings, forcible removal of the membrane, and cleansing by means of forceps or cotton. The only precaution to be taken is to avoid as much as possible hurting the subjacent mucous membrane. It is precisely for this reason that many advocate abstention, at least in cases of angina, since too energetic intervention might harm the mucous membrane. They endeavor to detach the pseudomembranous exudates by means of irrigations. At any rate, intervention is far less urgent than in cases of suppuration, for the pseudomembrane represents a barrier opposing the progress of the infection. As we have several times remarked, while warding off certain dangers the pseudomembrane may create others. By reason of its localization it may bring about serious functional disturbances and necessitate surgical intervention, such as tracheotomy, which is rather a palliative.

Treatment of Gangrenous Lesions. The more noxious the inflammatory exudates the more prompt and energetic intervention must be. In the case of a gangrenous or putrid lesion, operation must be performed as soon as possible, for the reason that the toxins produced by the microbes are so strong that the cells in contact with them cannot react, but die and undergo putrefaction, which adds new harmful substances to the medium. These putrid poisons being absorbed, impregnate the entire economy and rapidly produce a very grave general condition.

As soon as the existence of a putrid or gangrenous focus is determined, it must be freely incised and, if possible, the walls must be scraped and frequent irrigations practised. These rules are easily applicable to putrid pleurisies. They may also be employed in cases of pulmonary gangrene. Unfortunately, in the latter case intervention is more uncertain, and the individuals operated upon too often succumb, at times tardily, to uncontrollable hemorrhages.

For the treatment of gangrenes the author has for some time been in the habit of employing peroxide of hydrogen. Many patients suffering from erysipelas or a gangrenous phlegmon of the extremities recovered under this procedure. The author prescribes every day a local bath, lasting for an hour, in a 1:10,000 solution of potassium

permanganate. The limb is then surrounded with compresses of peroxide of hydrogen. In mild cases this treatment is sufficient. In grave cases a subcutaneous or interstitial injection of peroxide of hydrogen is given morning and evening. The author employs the commercial solution, to which is added an equal volume of a 4:1000 sodium bicarbonate solution. Morning and evening 5 c.cm. or 6 c.cm. sometimes 10 c.cm. of this solution, are injected through several punctures all around the sphacelated parts. The injections are given very slowly, so as not to distend the tissues too rapidly by the gas and to avoid penetration into some open bloodvessel. Under this treatment putrefaction is arrested and the eschars are soon detached.

When a gangrenous focus is limited the resistance of the organism is not yet overcome, and consequently operative assistance may be of service. If, however, the lesion is diffuse, if the tissues are simply the seat of a sphacelus in the absence of a focus, the diseased parts cannot be extirpated. Such is notably the case in gangrene of the extremities. When the lesions are extensive but superficial, for instance, as a result of lymphangitis and erysipelas of the lower extremities, if the general state is fairly satisfactory, recovery may be obtained by means of appropriate dressings, by the employment of antiseptics and subcutaneous injections of peroxide of hydrogen. Too often, however, the toxins produced in the necrosed parts give rise to serious symptoms and necessitate amputation of the extremity above the diseased parts. This operation is the only one available in cases of total or diffuse gangrene. Whether the accidents are due to an acute or chronic arteritis or are dependent upon the septic vibrio, there is no chance of recovery except by removing the entire diseased parts. In some cases, however, the apparently healthy tissues are already invaded and the gangrenous process reappears in the operative wound.

Gangrenes are not always hopeless as regards prognosis. An affection designated by the characteristic name benign gangrene of the bronchial extremities has long been known. We have reported observations of gangrenous mammitis and of curable gangrene of the eyelids which have terminated without causing any serious symptoms. Lastly, among gangrenous anginas there are some in which the limited sphacelus only slightly disturbs the general condition of the patient. In all these cases the indication is the same as for purulent exudates, and local intervention or antiseptics render the greater service.

Treatment of Nodular Lesions. The last form of inflammatory reaction consists in the production of nodules the extent of which is extremely variable. When small, the granulations are generally very numerous and disseminated, and intervention is impossible. When they are united in a mass they behave as a tumor and require the same treatment as the latter—that is, extirpation. Finally, when the mass, after having been caseated, is softened, treatment is the same as in cases of suppurating foci. In both orders of lesions the natural tendency is to open outwardly, but the opening is tardy and insufficient. We must, therefore, intervene, incise the focus, scrape the walls, extirpate the parts too profoundly altered, and then keep in contact with the focus modifying substances or antiseptics. Among the latter iodine preparations are most commonly employed.

It is not to be overlooked, however, that in tuberculosis surgical intervention has sometimes been the point of departure for an acute attack.

Patients who supported a local lesion fairly well have, in consequence of an operation, developed grave symptoms and succumbed to an attack of acute miliary tuberculosis.

Treatment of Hemorrhages. Hemorrhages occurring in the course of infectious diseases may be divided into two groups: Some are local hemorrhages produced in an inflamed part as a result of the too great intensity of morbid phenomena and the accidental alteration of bloodvessels. Hemorrhage may be slight or grave, transitory or recurring, but it is generally produced at one point or at a series of points close to each other. The second group comprises hemorrhages resulting from general modification of the organism. These are not necessarily serious. In a good many infections, small cutaneous hemorrhages occur which in nowise render prognosis unfavorable. Such is not the case, however, when multiple and repeated hemorrhages take place. We are then in the presence of the hemorrhagic forms of infections. To this group belong the putrid fevers of the ancients. In this case the treatment must be directed to modify the general state of the economy, and particularly the chemical constitution of the blood.

Hemorrhages Due to Local Causes. Hemorrhages arising from local causes may be due to particularly intense inflammation. Congestion in this case terminates in rupture. In other instances inflammation is mild, but occurs in an individual predisposed to local or general hemorrhages. Lastly, in a third group may be classed

those cases in which a morbid process involves a bloodvessel and ulcerates it.

Hemorrhages resulting from too great intensity of a reactionary process are frequent and, as a rule, of little gravity. They may be observed in the skin, in the mucous membranes, and in the organs. Infectious exanthemata and enanthemata, when somewhat intense, produce small vascular ruptures, especially in those parts in which the circulation is more or less embarrassed. When scarlatinal eruption is intense small patches of purpura, which have no prognostic value, are often observed, particularly in the lower extremities. Similarly, in cases of confluent variola, the pustules upon the legs and hands are sometimes filled with blood; their color changes; they become brownish, and are soon covered with black crusts. These small hemorrhages have no serious significance. They often seem to exercise even a favorable action upon the course of the local process.

Small hemorrhages are likewise produced in inflamed mucous membranes. At times they present a spotted aspect. For example, a mottled red patch occurs in the throat in cases of angina. In some cases, as the mucous membrane is less resistant than the skin, the blood flows out. In the case of coryza, epistaxis is the result; in the case of angina, laryngitis and bronchitis, some spitting of blood; in cases of gastritis or intense enteritis blood appears in the vomit and dejecta. The intestinal hemorrhages occurring at the beginning of typhoid fever must likewise be attributed to the great violence of the infectious process. As is known, their prognosis is generally favorable. Among the hemorrhages which may take place in parenchymatous organs, those interesting for the therapeutist are expressed by appreciable symptoms. In this connection two organs particularly deserve study: the lungs and the kidneys.

In cases of bronchopneumonia infarctions may occur in the inflamed nodules, but they generally remain unnoticed. More extensive infarctions give rise to bloody expectoration. In the kidneys, inflammatory hemorrhages are frequent and readily recognized by hematuria. In primary acute and in scarlatinal nephrites, hematuria is often very pronounced and sometimes represents the first morbid manifestation. It may occur, although seldom, in erysipelas. In this instance, however, it lasts longer than in scarlatinal nephritis without having any prognostic gravity. Hemorrhagic nephritis is altogether rare in other infections, except those attended by multiple hemorrhages indicating profound alteration of the organism.

Now, a few words in reference to hemorrhages dependent upon individual predisposition. Small ecchymoses in the lower extremities in the course of various eruptive fevers, measles, scarlatina, or variola occur in subjects having voluminous varices. The eruption of measles may also sometimes, here and there, assume an ecchymotic aspect. This occurs particularly in children suffering from whooping-cough and in men taking copaiba (page 434). In other instances the hemorrhagic tendency is explained by the state of the subject, who is suffering from a previous hemophilia, or who is under the influence of another infection or intoxication.

Hemorrhages resulting from the extension of an infectious process into bloodvessels are more important. In most cases this extension is effected so slowly as to permit the formation of a vascular thrombosis. If, however, the course is rapid or particularly intense, the vessel is opened, and the hemorrhage thus occurring may be serious enough to cause death, as it may, for example, happen in the third stage of typhoid fever.

Hemorrhages Due to General Causes. Along with hemorrhages arising from local causes are to be placed those dependent upon a general modification of the organism. We shall divide them into three groups. A hemorrhage may represent a symptom of infection. Such is the case in purpura. It may depend upon the lesion of an organ which plays an important rôle in the coagulability of the blood. Such is the case in infectious grave icterus. Finally, and this is the group which we must particularly study, it may result from special virulence of the pathogenic germ. They then constitute a particular form of the disease which, in certain cases, differs entirely from the classical type. Thus, hemorrhagic forms of measles, scarlatina, and typhoid fever have been described. These facts are, however, exceptional, and the most interesting disease from this standpoint is undoubtedly variola. In hemorrhagic variola bloody effusions may occur in any tissue and organ. There may be observed purpura, cutaneous ecchymoses, and bullæ, subconjunctival and buccopharyngeal ecchymoses, epistaxis; gastric, intestinal, uterine, renal, or pulmonary hemorrhages, and extensive bloody infiltrations beneath the skin and in the serous membranes. However multiple they may be, however many parts of the body they may affect, and however grave in character, hemorrhages do not occur at all points of the organism. The alteration of the blood does not, therefore, explain the phenomena completely. We must admit either a predisposition

or some concomitant lesion in the parts which become the seat of the bloody effusion.

Although hemorrhagic infections mostly belong to the group of general infections, a localized focus may give rise to toxins sufficiently abundant and active to impregnate the entire economy and cause hemorrhages at points distant from the primary lesion. Dr. Dieulafoy has called attention to facts of this kind by showing that, in certain lesions of the intestine, and notably in appendicitis, noxious substances are elaborated which explain the occurrence of hemorrhages at distant points—for example, hematemesis.

The preliminary considerations above presented show us how infectious hemorrhages may be divided theoretically. They establish at the same time that, in the majority of cases, the process is complex. The therapeutist must, therefore, frequently resort to local medication as well as to medication capable of modifying the general state.

Therapeutic Indications. The first indication is to prescribe rest and immobility. A movement may cause detachment of the clots occluding the open vessels, and thus renew the hemorrhage. In the case of a patient for whom baths have been prescribed, these should be discontinued. If the patient is agitated or delirious, it will be advisable to prescribe soothing medications, for instance, opium or morphine, so as to insure complete quiet. Opium is generally indicated when the patient coughs, even though no bronchial or pulmonary hemorrhages exist, for the effort involved in coughing may detach the clot. It should be remembered that whooping-cough is of itself sufficient to produce hemorrhages. These precautions being taken, it would be well to further prescribe substances which increase the coagulability of the blood. Even when the question is one of local hemorrhages, the dyscrasic modifications resulting from infection tend to maintain or aggravate the flow of blood. For this purpose acid beverages have long been in use. Citric acid or sulphuric acid lemonade may be prescribed. Haller employed in hemorrhagic variola the acid elixir bearing his name and which is nothing else than a dilution of sulphuric acid. Sydenham asserted that sulphuric acid, given in small beer, was the specific medicine for confluent and hemorrhagic variola. At present use is made only of Rabel's water (Eau de Rabel) which, as is known, is a mixture of 100 parts of official sulphuric acid, 300 parts of alcohol (at 90° F.), and 4 parts of petals of red poppy. Thus is formed an ethyl sulphate the taste

of which recalls that of old brandies. One may prescribe a lemonade containing 5 per 1000 of Rabel's water. However, the author's experience with this medication in cases of hemorrhagic variola has not been encouraging.

At present we possess two medicines which seem capable of increasing the coagulability of the blood: one of them is calcium chloride. The author has frequently employed this salt in the treatment of hemorrhagic infections and notably in hemorrhagic variola. In two or three days hematurias are arrested, as well as enterorrhagias and metrorrhagias. In spite of these ameliorations, however, many patients die. As a few patients suffering from pustular variola with hemorrhages recovered, and as the medication is inoffensive, the author thinks that it is advisable to resort to it in all such cases. It seems to be applicable even to all diseases in which hemorrhages are due to defective coagulability of the blood. Chloride of calcium thus seems destined to occupy a permanent place in general hemostatic medicines. It is therefore necessary to first determine its posology. This salt is not very toxic; injected into the veins of a rabbit it proves fatal when 100 c.cm. of a 1 per cent. solution, that is, 1 gram of the medicine per kilogram of animal is introduced. This salt, however, is caustic: beneath the skin it produces necrosis and slough. The hypodermic method cannot, therefore, be utilized. It must be introduced by the digestive tract. Either the anhydrous or the crystallized chloride may be prescribed indifferently. It should be remembered, however, that the former is twice as strong as the latter, which, as is known, contains six molecules of water of crystallization. The doses above indicated are those of the crystallized chloride of calcium. These doses should be reduced one-half if the anhydrous chloride is prescribed. When dissolved in water or in a julep, this salt has a very disagreeable flavor, recalling that of sea water, leaving in the mouth a metallic taste. It is, therefore, well to prescribe it in some excipient which will mask its taste. Rabuteau prescribed 5 grams of calcium chloride in 400 grams of simple syrup and 100 grams of peppermint-water. The daily dose of 4 grams (℥j), which is at times prescribed, seemed to him by far too strong, and he advised the administration of from 20 cg. to 1 gram a day (3 to 15 grains).

When hemorrhages must be arrested these doses are insufficient. They may be considerably increased without inconvenience. The author has begun with giving 4 grams (℥j). Later, when treating a

non-vaccinated child, one year old, he administered from 1 to 1½ grams (15 to 22 grains); the child recovered. The author then thought that the doses might be increased for adults, and he cautiously gave as much as 12 grams (℥iij) in twenty-four hours. This result demonstrates the harmlessness of the medicine which, contrary to the opinion advanced by some authorities, exercises no purgative action even when given in large doses. At any rate, the author has come to recognize that it is useless to prescribe such considerable quantities; 4 grams (℥j) a day suffice. The best method of administering the medicine is to dissolve it in a potion containing syrup of bitter orange-peel and including, like the potion of Todd of the Codex, rum and tincture of cinnamon.

The following may be prescribed:

Crystallized calcium chloride	4 to 6 grams	(℥j–jss)
Syrup of bitter orange-peel	40 "	(℥j)
Old brandy or rum	30 "	(℥j)
Tincture of cinnamon	5 "	(℥j)
Distilled water	50 "	(℥ij)

This potion is by no means disagreeable. It may readily be modified by increasing the quantity of rum and, if the taste is unpleasant, by omitting the tincture of cinnamon. A potion without alcohol must be prescribed when a renal lesion is suspected. The syrup of bitter orange-peel suffices to mask the taste, but not as completely as in the formula above given. Chloride of calcium has a by no means less important employment in the treatment of hemorrhagic nephrites. In cases of primary or secondary, and notably of scarlatinal nephrites, a potion containing from 3 to 4 grams of calcium chloride rapidly diminishes hematuria. In most cases the urine contains no blood at the end of two or three days. In several cases the author noticed the reappearance of hematuria when the medicine was discontinued. As, however, it is admitted that the salts of calcium diminish the coagulability of the blood at the end of a few days, instead of increasing it, the author has constantly suspended its use after four or five days. If necessary, it may again be prescribed after an interruption of three or four days.

Since the contributions of Dastre and P. Carnot, gelatin also is known to have the property of increasing the coagulability of the blood. Experiments upon animals have demonstrated this. The method consists in injecting the substance into the veins. One hesitates to apply the method in man. The subcutaneous channel has,

therefore, been employed. Physiologists contend, however, that under these conditions the coagulability of the blood is not modified for the reason that the substance is not absorbed. The author has tried subcutaneous injection of gelatin in several cases of hemorrhagic variola. In one of the cases the results were excellent, since the symptoms improved and the patient recovered. The injected liquid, however, became the starting point of a gangrenous phlegmon which raised the entire skin of the abdomen and healed only after a considerable period of time. This suppuration is explained by the infected condition of the skin in variola. It is interesting to note that the liquid which was discharged by an incision contained a great amount of unaltered gelatin.

Satisfactory results may be obtained when the chemical modifications of the blood in hemorrhagic infections are discovered. Now that coagulating ferments and fibrinogenous substances are easily prepared, it might be possible to combat a hemorrhagic tendency by means of organic extracts. In this connection the condition of the liver should, perhaps, receive more attention than has hitherto been given to it. At the necropsy of individuals succumbing to hemorrhagic variola the author has always detected far more profound and extensive hepatic lesions than in cases of confluent variola. It may, therefore, be questioned whether it would not be useful to struggle against the hepatic insufficiency by means of opotherapy.

Hemorrhages may be combated by producing vasoconstriction. This is obtained indirectly by revulsion, cuppings, sinapisms, and cold beverages. Vasoconstriction may also be effected by certain medicines, chief of which is ergot. The hemostatic action of ergot, which is doubted by so many, seems to me incontestable. It is not, as has been asserted by some, the muscular fibres of the uterus alone that are influenced by it. Nevertheless, ergot seems to the author contraindicated in fevers characterized by a gangrenous tendency in which the nutrition of certain parts seems to be endangered. For it should be well kept in mind that ergot contains substances which of themselves are capable of inducing sphacelus. This medicine is particularly useful when the general state is satisfactory and when the hemorrhage to be combated is confined to one viscus. The author has obtained satisfactory results in the treatment of hemorraghic nephritis, particularly that form following scarlatina. Two grams of Bonjean's ergotin, or 1 gram of Yvon's solution of ergot, or 1 mg. of Tanret's ergotinin may be prescribed. The author gen-

erally gives one gram of the solution of ergot for three days in succession. This medicine has the advantage of diminishing hematuria and inducing abundant diuresis, which assures organic depuration. Its action appears to the author, however, to be less certain and constant than that of calcium chloride, to which he now gives preference.

Ipecac is said to favor coagulation by modifying pressure, viz., by reducing it. This medicine is applied particularly in hemoptysis. Ten centigrams are given every half hour, amounting to two or three grams for the twenty-four hours. When the seat of the hemorrhage is accessible, certain substances which promote hemostasis, either by inducing vasoconstriction or by stimulating coagulation of the blood, may be deposited upon it. The former effect may be secured by the application of very cold or very hot fluids. Cold injections of water as well as hot injections at 118.4° or 122° F. (48° or 50° C.) are daily employed against uterine hemorrhages. They may likewise be resorted to for combating nasal hemorrhages. Hot enemas also may be given. When hemorrhages occur on the surface, heat may be applied in the form of a hot-air current. This method is very efficacious.

Cold may likewise be employed. When the blood proceeds from a deep-seated organ it suffices to apply upon the corresponding region an ice-bag. Fredericq's experiments tend to demonstrate that cold rapidly induces, by reflex action, vasoconstriction of parts subjacent to that which receive the influence. Thus an anemia eminently favorable to coagulation is produced. Certain medicines act as local vasoconstrictors, and among the number is antipyrin. When dusted upon a bleeding mucous membrane, antipyrin often arrests the flow of the blood, and thus renders great service in combating nasal or uterine hemorrhages.

Caustics form a transition between the two groups of hemostatic medicines, since they produce vascular constriction and, coincidently, favor coagulation by precipitating albumins. Hemorrhage may be arrested by touching the diseased part with silver nitrate or by placing upon it a compress saturated with zinc chloride solution. The substance most frequently employed for this purpose is perchloride of iron; but it is gradually falling into disfavor, because solutions of it induce necrosis, and mortification, and small sloughs, which may hinder evolution of the disease. Among the astringents employed as hemostatics we may also cite alum, which represents

the most active principle of Pagliari's hemostatic solution (alum 10, benzoin 50, water 100).

The astringents of vegetable origin seem to be free from the inconveniences inherent in mineral astringents. The most important is tannin, which may be used in its pure state, or various substances in which it is found. Injections and irrigations with an effusion of walnut leaves are often employed to arrest slight hemorrhages. It is necessary to remember that tannin, which is a vasoconstrictor in small doses, becomes a vasodilator in large doses. It may be employed in vaginal injections and enemas. The preparations of rhatania may often be substituted for it, the root containing 43 per cent. of tannin. In cases of intestinal hemorrhages in the course of variola the author has obtained excellent results by giving large enemas of 500 grams (1 pint) of boiled salt-water containing 6 grams (℥jss) of extract of rhatania morning and evening. A new method, initiated by Dr. Carnot, consists in increasing the coagulability of the blood by spreading gelatin solutions upon the diseased surfaces. This substance possesses the double advantage of being hemostatic and of representing a sort of aliment for the cells of the organism. It has the inconvenience of being a good culture medium for microbes. Hence, some antiseptic is often associated with it: 0.5: 1000 solution of corrosive sublimate, or a few drops of formol are added to the gelatin solutions, thus rendering them absolutely unassailable by bacteria. To obtain efficacious hemostatic action, it is necessary to employ a 10 per cent. gelatin solution and sterilize it twice at 212° F. (100° C.) for fifteen minutes each time. Care should be taken not to raise the temperature too high, otherwise the gelatin will lose its characteristic property and become a liquid. These solutions are employed either in local applications upon a bleeding wound or mucous membrane, or in intranasal or intravaginal injections. The author has frequently utilized vaginal injections of gelatin water in the treatment of metrorrhagias which are so common and often grave in variola. Owing to the addition of corrosive sublimate he has never observed the slightest infectious accident. It may, therefore, be concluded that gelatin is an excellent local hemostatic. While the author has expressed some reservation concerning its action upon multiple hemorrhages and regarding the inconvenience, at least in certain cases, of its subcutaneous introduction, there can be no doubt as to its efficacy in local treatment.

There is another substance which arrests hemorrhages admirably,

that is, peroxide of hydrogen. A compress saturated with the commercial solution is applied to the bleeding part. The acid contained in the liquid favors hemostasis, but renders the treatment somewhat painful.

By means of the various procedures above indicated, it is possible to successfully combat diverse hemorrhages. It is well to remark, however, that this is simply struggling against a symptom, against the result of an infectious disease upon the gravity of which prognosis entirely depends. It is certain that in hemorrhagic variola the gravity is not due to the hemorrhages. They simply express the profound intoxication to which the organism succumbs. On the other hand, when a hemorrhage results from a focal lesion, the latter being too intense or too profound, hemostatics are then directed against the very cause of the accidents. All those that we have mentioned are useful, but it is evident that the ideal treatment is surgical. The bleeding vessels should be ligatured. Surgical applications, however, are seldom available in the hemorrhages of infectious diseases. The attempts that have been made in typhoid fever are far less rational and efficacious than the operations directed against perforations. The fact is that a large ulcerated vessel is seldom found. In most cases the hemorrhages are multiple or capillary, and operation is evidently out of the question. Surgical intervention is serviceable only in chronic infections. In cases of renal tuberculosis, nephrectomy has often been the only remedy for the persistent hemorrhages.

Therapeutics of Fever.

Fever constitutes such an essential feature of acute infectious diseases, and, by its course, generally expresses so faithfully their evolution that physicians, mistaking the effect for the cause, have at all times striven to check the febrile movement. Modern advances in pathological physiology enable us to better comprehend the succession of events. Hence, the question whether fever should be combated was laid before the last International Medical Congress.

In order to give a solution to this important problem of therapeutics, we must carefully distinguish the febrile process, viz., the increase in the intraorganic chemical acts, from its most apparent result, that is, hyperthermia. To oppose the chemical metabolism going on within an infected organism would be checking a salutary

reaction—salutary at least in most cases, for, as we have repeatedly stated, the organism does not always exactly proportion its efforts to its needs. It is at times necessary to moderate the intensity of chemical changes. For this purpose antipyretics render most valuable service. This is what occurs especially at the end of infections and during convalescence. It seems that the nervous system, excited by the disease which had just terminated, has become too sensitive; the slightest cause gives rise to a febrile reaction which must be combated, notably by antipyrin.

In the course of acute infections antipyretics are generally prescribed only when they can act upon the cause of the fever. Specifics respond to this indication. The type of this class is represented by quinine salts. It is to-day admitted that these salts are extremely toxic for the protozoa. They arrest the evolution of Laveran's parasites, and consequently the reaction which characterizes the paroxysm. It would be an error to say that quinine is an antipyretic. It prevents the return of the fever because it arrests the infectious process which causes it. Hence, it produces no action against the majority of other hyperthermias. Enormous doses of quinine have been given to typhoid and tubercular patients without lowering their temperature so much as one-tenth of a degree.

Salicylate of soda seems to act in the same manner. It extinguishes rheumatic fever because it checks the infectious process. It is the same with mercury and iodide, which combat syphilitic fever. To speak of antipyretics in all such cases would be no more exact than to speak of an antipyretic operation when a pyogenic fever is arrested by opening a suppurating focus. The fever is suppressed because the cause of the accidents has been removed.

Although in the majority of cases it would be a mistake to combat the febrile process, it should not be concluded that it is contraindicated to combat its principal result—hyperthermia. I have endeavored to make it clear that elevation of temperature is the result and sign of increased activity in the chemical acts. A larger amount of heat is produced, but the excess is at the same time dissipated, as is proved by the increased radiation of heat. It is, therefore, indicated to combat hyperthermia by increasing radiation. The best method is by cold bathing.

Cold and Lukewarm Baths. From the earliest antiquity baths have been given in certain infections. A lukewarm bath was commonly employed, notably in pneumonia. It was also a lukewarm

bath that was first employed against typhoid fever by Currie in the eighteenth century, and at the beginning of the nineteenth by Chomel, Récamier, and Rayer. Cold water had, however, already been praised by Bartholin, more than two hundred years ago, against pneumonia. The method, however, does not seem to have had great success, for about fifty years ago physicians timidly utilized cold lotions, and sprinkling, and the wet sheet. Few of them ventured to bathe their fever patients. A few attempts were made in favor of cold baths by Giannini (1805), Chomel, Récamier, Jacquez and Leroy. It was, however, only after the labors of von Ziemssen and Brand (1861) that antipyretic balneotherapy entered into therapeutics in a definite manner.

Von Ziemssen prescribed baths that rendered the body gradually colder. Bouchard adopted a similar method. In order to avoid the influence exerted upon the nervous system and the vasoconstrictors by cold water, he caused the patient to be placed in a bath the temperature of which is only two degrees Centigrade lower than that of the body. Then he progressively lowers the temperature of the bath to 86° F. (30° C.), never below that point.

By the method which bears his name, Brand produces a violent excitation of the nervous system. Let us consider the rules laid down by him for the treatment of typhoid fever. They are applicable, with slight modifications, to all infectious diseases.

As soon as the temperature of the patient exceeds 102.2° F. (39° C.), he is plunged into a bath at 68° F. (20° C.); at times, if the case is grave and the fever intense, into a bath at 64.4° F. (18° C.). Certain precautions are to be taken at the same time. Borated vaseline is applied to abrasions and pustules. In order to avoid too violent respiratory disturbance, cold effusions are applied to the face and chest, and the patient is then taken in the arms of the nurse and placed in the bath-tub. The tub should contain sufficient water to cover the shoulders, and it is advisable to renew the water for each bathing. When the patient is in the bath-tub he receives three cold effusions at 50° F. (10° C.), at the nape of the neck. These effusions should last three minutes each. Frictions upon the body, except the abdomen, are at the same time to be made. Finally, a small amount of vinous lemonade is to be given to the patient. The bath lasts fifteen minutes. If he should experience chills the patient may still be left in the water, but not for more than two or three minutes longer. When once out of the

water he must be rapidly wiped and then enveloped in blankets and warmed by means of hot water bags applied to the legs and feet. Half an hour later he must be given milk and bouillon.

If the patient does not sleep, or if his sleep is agitated, Brand advises, during the intervals of the baths, application of compresses of water at 50° F. (10° C.) to the chest and abdomen, to be renewed every five, ten, or fifteen minutes, according to the intensity of the fever. Tripier and Bouveret prefer large cold poultices upon the abdomen. The bathing, to be efficacious, must be instituted as soon as the diagnosis of typhoid fever is made. If there is any doubt as to the nature of the disease, bathing may still be resorted to, provided it is discontinued if further developments prove the case not to be typhoid. When the physician is called to the side of a patient who has been suffering from typhoid fever for three weeks, the cold bath is useless, and Brand himself then prefers lukewarm baths.

The baths must be started as soon as the temperature of the patient reaches 102.2° F. (39° C.), and the temperature must constantly guide the physician. The temperature must be taken every three hours. When it rises above 102.2° F. (39° C.) a bath is given. When, at the end of three hours, the temperature has not risen to that point, the corresponding bath is omitted. The case is to be managed in this manner until the fever falls below 102.2° F. (39° C.) definitively. At the beginning the temperature rises quite rapidly. The patient, therefore, takes the baths regularly every three hours. As they are not interrupted during the night, he consequently takes eight baths a day. Later he skips several. In certain cases fever is very intense and does not yield to balneotherapy. Brand then advises, in addition, the permanent employment of cold compresses. Tripier and Bouveret resort to the wet sheet. Chauffard gives the baths at shorter intervals; Juhel-Renoy gives one every two hours at 59° to 60.8° F. (15° to 16° C.).

In typhoid fever cold bathing has a certain number of contra-indications. In the first place, age is to be taken into account. In children above two years of age it is well to begin with baths at 77° F. (25° C.); below that age, lukewarm baths at 86° or 89.6° F. (30° or 32° C.) must be given three or four times in twenty-four hours, each lasting from five to eight minutes. Brand does not advise cold bathing if the patient is more than fifty years old. According to my personal observations, I believe that this limit

should be lowered. It may broadly be stated that, in all infections, cold baths are dangerous above forty years of age. They may, nevertheless, be employed at this age if the circulatory and the respiratory apparatus of the individual are in a perfect state. As a matter of fact, before instituting balneotherapy, the physician must carefully examine these two apparatuses. Valvular lesions of the heart, chronic myocarditis and pericarditis, arteriosclerosis, as well as chronic bronchitis, dilatation of the bronchi, tuberculosis, and, above all, pulmonary emphysema, are contraindications to the balneotherapic method, even to the method of graduated cold baths. Next, the nervous system must be taken into account. In hysterical individuals the bath may provoke an attack. In that case it must be discarded. In certain neuropathic persons it causes fainting or paroxysms of suffocation with a certain degree of asphyxia and cyanosis. In such cases a cold bath is likewise contraindicated. Moreover, some patients have such repugnance to bathing that after they have been given one their temperature is not lowered, but, at times, even a rise occurs. By insisting a little, the physician sometimes may render the bathing method acceptable to such individuals; otherwise, it is better to abandon the balneotherapic procedure.

These considerations are applicable to all infections. Here are some concerning particularly typhoid fever: Intestinal hemorrhages and peritoneal manifestations demand absolute rest, and baths should therefore be suspended. Pneumonia is not a contraindication, except when the heart shows signs of weakness. We here touch a much disputed problem. What course is to be followed in cases of myocarditis? The perusal of classical works leaves the physician in an embarrassed state of mind, for equally competent authorities have advanced contrary views. I believe that, at the beginning, when myocarditis is expressed simply by acceleration in the heart-beats and weakening of the pulse, bathing should still be employed, provided the heart is sustained by medicines such as caffein. Should the slightest fainting occur during the bathing the method must be suspended definitively. If the myocardium seems to be affected, lukewarm bathing may be tried; if it is well borne, the succeeding baths may be given gradually colder. At a more advanced period, when auscultation reveals a *bruit de galop*, and especially the fetal rhythm, then balneotherapy seems to be a dangerous method, for the reason that the movements of the patient may provoke syncope

and sudden death. The writer believes that, under such conditions, all kinds of baths should be avoided.

Cold baths do not abridge the duration of typhoid fever, but they palliate certain symptoms and diminish the death-rate. There is little, if any, stupor; the tongue is moist, diarrhea is moderate, diuresis is more abundant, the appetite is not completely lost, so that the patient takes nourishment with pleasure. Delirium is rare, and, instead of somnolence and the muttering observed in ordinary cases, the patient enjoys a quiet and refreshing sleep after a bath.

The course of the temperature is profoundly modified. Brand divides it into three periods: the period of resistance, during which the temperature is but slightly modified; then the period of remission, and, finally, that of defervescence. The longer the first period lasts, the longer and more rebellious will be the case. If the temperature yields to the first baths, the fever to be dealt with will prove to be a mild one. The cold bath also acts upon the circulation and respiration; it stimulates the action of the heart and strengthens the pulse; it diminishes bronchitis and relieves pulmonary congestion.

As already stated, the death-rate is considerably reduced by this treatment. It is not necessary to cite numerous statistics; it will suffice to state that out of 19,017 observations tabulated by Brand the mortality did not exceed 7.8 per cent. In the Bavarian army, in which the method is practised in all its rigor and is instituted as soon as the disease is suspected, the death-rate reaches hardly 1 per cent. Although cold baths are at present frequently employed according to the rules of Brand, they have often been modified. Thus, the employment of baths at 82.4° F. (28° C.) has gradually become the current practise in the hospitals of Paris. The baths are given every three hours, when the temperature exceeds 102.2 or 103.1° F. (39° or 39.5° C.). When baths at 82.4° F. (28° C.) are given, it is useless to employ previous cold effusions or friction during the bath. This method is more readily accepted by the patients, it requires less caution, and gives satisfactory results. I have recourse to it in benign cases, and I employ no other in the case of children.

Cold baths do not act merely by abstracting heat. On the contrary, their action is far more complex. This question has been well studied by Liebermeister. We borrow from him the following

figures, which show the difference of action of a bath at 71.6° F. (22° C.) from that at 82.4° F. (28° C.):

	In a Bath at 71.6° F. (22° C.).	*In a Bath at 82.4° F. (28° C.).*
In 5 minutes the patient loses	122 calories.	33 calories.
In 10 " " " "	165 "	44 "
In 15 " " " "	192 "	50 "
In 20 " " " "	208 "	52 "
In 30 " " " "	342 "	56 "

If the principal object was to abstract heat, the bath at 82.4° F. (28° C.) should be rejected without hesitation; but at present the influence of hyperthermia is no longer so much dreaded. It is known that the disturbances and lesions formerly attributed to high temperature are in most cases due to toxins. Cold baths produce satisfactory results, not merely by lowering the temperature, but exercising a favorable influence upon the various apparatus of the entire organism. First of all, the nerve terminations of the skin are influenced by the bath, and their dynamic modification reaches the centres. The very cold bath thus gives rise to a violent excitation; the lukewarm bath has a sedative action. In both cases the function of the nervous system is regulated, and amelioration in the activity of all the tributary organs results. The heart largely participates in the benefit of this happy influence. In the case of cold baths, the cutaneous vasoconstriction raises the blood pressure, and thus modifies the activity of the myocardium. Circulation is, therefore, favored in the lungs and kidneys. Hence, diminution in pulmonary congestion and increase in diuresis, as well as greater activity in general oxidation, result. All these changes explain how the bath diminishes the intoxication of the organism. It accomplishes this by regulating nutrition, by favoring the action of the liver and the emunctories, notably the kidneys. The experiments of Drs. Roques and Weil demonstrated that the urinary secretion is not only increased in amount but also in toxicity. Thus a great quantity of toxins is carried away and the organism purified.

Brand's method, which was at first applied to typhoid fever, is now employed in a great number of infections. The baths may be given whenever the temperature is very high, not so much because of the hyperthermia as for the intensity of the morbid phenomena which produce and entertain it. The baths must likewise be resorted to when the nervous system is profoundly affected, when the pulse is very rapid and the urine scanty. The physician must always

be guided by the gravity of the phenomena in choosing between lukewarm, 82.4° F. (28° C.), and cold baths, 69° or 64.4° F. (20° or 18° C.). The latter are especially indicated when the nervous system is profoundly affected, whether the phenomena indicate depression, or, on the contrary, too violent excitations, such as delirium tremens, are present. Finally, the satisfactory results obtained by cold baths in the treatment of cerebral rheumatism have long been recognized.

In our hospital we employ the bath at 82.4° F. (28° C.), less frequently at a lower temperature, in cases of scarlatina and erysipelas whenever the temperature remains longer than usual around or above 104° F. (40° C.). This treatment is less frequently available in measles, for the gravity of the latter disease depends simply upon pulmonary complications. We shall again refer to this subject.

Balneotherapy is also indicated in measles, scarlatina, and variola when the eruption is not well developed. The author prefers warm baths at 89.6° or 93.2° F. (32° or 34° C.), and in grave variola or measles, mustard baths. At the beginning of all eruptive fevers we frequently see serious general manifestations while the eruption is as yet hardly noticeable. The eruption does not come out as rapidly and with the same intensity as in fortunate cases. A few baths hasten the appearance of the exanthema and palliate the grave symptoms. In variola also, as we have already stated, excellent results are obtained by the same method. The author gives lukewarm baths to which some corrosive sublimate or naphthol is added. Notwithstanding its lesions, the skin bears this mode of treatment well. It exercises a marked action upon the pyogenic bacteria which, at a certain period of evolution, invade the pustules.

Among the infections for which baths are available there are three which require special attention. These are scarlatina, pneumonia, and erysipelas. Hyperpyretic scarlatina is generally described as the type of malignant scarlatina. If we refer to our statistics we find that the frequency of this form, at least in the adult, has been somewhat exaggerated. We have received in our wards, especially in 1899, grave cases, several of which rapidly ended in death. In the majority of the cases, however, the temperature was not extremely high. It is not, therefore, safe to be guided exclusively by the course of the temperature. The general state of the patient furnishes more reliable indications. The general state likewise directs the therapeutics of pneumonia. All grave cases must not, however, be indiscrimin-

ately treated by baths. This medication must not be resorted to in the aged or in arteriosclerotic individuals, or those suffering from heart lesions and Bright's disease. These are substantially the same contraindications which we have pointed out with regard to other diseases. The reason we emphasize the point is that it is precisely under these conditions that the gravest cases are observed and that the physician is tempted to prescribe baths. What is more peculiar to pneumonia is the danger of giving rise to collapse in case both lungs are involved. In fortunate cases, under the influence of the bath, respiration becomes easier, expectoration more profuse and free, cyanosis disappears, and diuresis is more marked; at times a veritable polyuria is produced. Hence the termination of the disease differs from that observed when the evolution is left to itself. The crisis is replaced by a slow defervescence, which is probably due to the fact that the toxins, far from being accumulated during the disease, to be suddenly rejected at the moment of the termination, have been eliminated in a continuous manner.

Baths are currently employed in the treatment of bronchopneumonia. In this case cold baths have been almost entirely abandoned, for they readily give rise to collapse, especially in young children. Graduated cold baths may be used. They may be given at two degrees lower than the temperature of the patient and progressively lowered to 82.4° F. (28° C.). Their duration must not exceed five minutes. More frequently lukewarm mustard baths are prescribed, especially for children. Finally, since the contributions of Dr. Renaut, warm baths at 100.4° F. (38° C.) are often employed. The child remains in it from ten to twenty seconds, and during all this time, cold compresses are applied to the head. The baths rapidly palliate the bronchial manifestations, but they produce hardly any effect upon the pulmonary lesions. Their action upon the general state is excellent, but the hot bath is somewhat depressing. It must be avoided in adynamic cases or when cardiac disturbances are present.

The author frequently employs lukewarm baths in the treatment of erysipelas. In cases of circumscribed erysipelas of the face unattended by grave general phenomena the bath is useless. In spite of the temperature of 104° F. (40° C.) defervescence is rapidly produced. If, however, fever persists, if certain alarming manifestations, such as adynamia, delirium, and agitation are observed, or if the inflammatory lesion spreads, a bath at 82.4° F. (28° C.) should

then be given every three hours whenever the temperature exceeds 103° F. (39.5° C.).

In cases of wandering erysipelas, baths at 82.5° F. (28° C.) are likewise indicated. They should be given systematically every three hours, regardless of fluctuations in the temperature, for in these wandering forms very wide oscillations are observed, and even intermittent types are sometimes encountered. Baths are similarly successful in delirium. The author generally employs lukewarm baths. Morning and evening he prescribes a bath at 93.2° F. (34° C.), which lasts from thirty to forty-five minutes. Its sedative effect upon the nervous system is very remarkable. Warm baths succeed very well in erysipelas of children and of the newborn. In the latter, regardless of the seat of the lesion, three daily baths at 89.5° or 93.2° F. (32° or 34° C.), lasting six or eight minutes, constitute the best method.

It is well to once more recall the danger of baths for individuals above forty years of age. As erysipelas is a disease occurring mainly after this age, the author believes the following precept should be emphasized: lukewarm baths may be given between the ages of forty and fifty years; after fifty years they should not be prescribed except for robust individuals presenting no lesions of the circulatory or respiratory apparatus.

Chemical Antithermics. Chemical antithermics act in three ways: they exercise a sedative action upon the nervous system; they diminish the protoplasmic activity of the cells; they modify the function of the red blood corpuscles. Of these three actions the first is contestable; it results simply from the fact that antithermics are, as a rule, analgesics. The second is bad, for increased functional activity of the cells represents a necessary reaction which should be moderated only under certain circumstances. The third is worse, for it consists in the formation of methemoglobin, which causes cyanosis. This last influence is particularly manifest when kairin, thallin, or acetanilid (antifebrin) are employed. These products are, therefore, almost completely abandoned, and only three antipyretics are at present made use of: quinine, antipyrin, and salicylic acid and its derivatives.

The successes obtained by quinine in the treatment of malarial fevers, in which it acts as a specific, have too easily led to the belief that this substance is a universal febrifuge. In typhoid fever as well as in erysipelas, pneumonia, and variola, the author has repeatedly observed that large doses of quinine salts may be administered with-

out producing any noticeable change in the temperature. One gram and a half or two grams are required in typhoid fever in order to effect a reduction of temperature. In view of these failures, some authors have stated that quinine regulates rather than lowers the temperature. Its administration must, therefore, be reserved for those cases of fever which present wide oscillations—*i. e.*, fevers of an intermittent type, like malarial fever. This remark is correct for some cases. Thus, for instance, in typhoid fever, after having remained at a certain point during the stationary period, the temperature often presents wide oscillations at the moment of termination. When fever is continuous the author has never found quinine efficacious. At the time of the oscillations the administration of this alkaloid appeared in some cases to bring the temperature to the normal. Hence, the author believes that it is useless to prescribe quinine during the stationary period. This medicine should be reserved for the third period. If the temperature then presents an amphibole stage and does not return to the normal, quinine should be prescribed in decreasing doses for three days in succession, four or five hours before the expected return of the paroxysm. The author prescribes 1 gram the first day, 75 cg. the second, and 50 cg. the third day. It is to be borne in mind, however, that this method is not infallible and that quite often fever does not yield to the action of quinine even at this period.

The author has likewise been convinced of the inefficacy of quinine in the treatment of hectic fever of tubercular subjects and of the fever of erysipelas, even when its course assumes the intermittent type, falling to 98.5° F. (37° C.) in the morning, to rise to 104° F. (40° C.) in the evening. Lastly, in symptomatic intermittent fevers quinine at times lowers the temperature. The result is not very marked or very durable, however, so that this medicine may serve to make a differential diagnosis between symptomatic intermittent and malarial fevers.

Antipyrin has a far more marked influence upon the febrile process. It often lowers the temperature; but it accomplishes this by diminishing oxidations, consequently, by hindering one of the reactionary procedures employed by the organism. Hence, its use is but exceptionally indicated. The author finds only a few cases in which this medicine is serviceable. The first is influenza. Antipyrin must be given mixed with quinine. The author prescribes 1 or 2 grams of the first with 75 cg. or 1 gram of the second. When

administered at the beginning of influenza this medication often succeeds in arresting the disease. It is almost a specific. Again, those tubercular patients who suffer from fever are often benefited by the use of antipyrin, at least in those cases in which it does not cause too much sweating. Its action upon the fever of tubercular subjects is so marked that Dr. Landouzy thinks, with good reason, that it may throw light upon a doubtful diagnosis in acute cases. When the physician is not sure whether he is dealing with a typhoid fever or an acute miliary tuberculosis, the administration of antipyrin, if it be followed by a well-marked defervescence, will lead him to assume that the case is tubercular. At any rate, antipyrin acts in all forms of tubercular fever, even against hectic fever. Its action, however, is transitory. The author has seen tubercular cases in which no treatment had succeeded in lowering the temperature, become completely apyretic under the influence of this medicine. At the end of four or five days, however, fever reappeared, and, although the dose was increased to 3 and 4 grams in twenty-four hours, the effect seemed completely exhausted. Although transitory and in nowise affecting the process itself, but only one of its effects, the action of antipyrin seems to the author sufficiently marked to give the substance a permanent place in the therapeutics of tuberculosis.

While antipyrin is useless in the stationary period of infections, it renders true service at the terminal period and during convalescence. In many cases fever survives the disease. The morbid symptoms seem to have disappeared, but the temperature does not become normal. This fact is due to the reactionary susceptibility of the organism induced by the infection. Under these conditions the organic combustions exceed the requirements of the system. Antipyrin, by modifying oxidations, reduces metabolism to a degree corresponding to the wants of the economy. Likewise, during convalescence the slightest cause suffices to raise the temperature. A febrile paroxysm may supervene, even without any noticeable cause. Antipyrin is then indicated, inasmuch as this fever of convalescence is dependent upon the same mechanism as the lingering fever at the end of infections, and should be treated in the same manner.

A new antipyretic, pyramidon, has recently been praised, and may be employed under the same conditions as antipyrin, but in smaller doses. This substance has given satisfactory results in some of the author's cases. Its advantage consists in its very quick elimination. Thirty and fifty centigrams of pyramidon may, therefore, be pre-

scribed every three hours, and as much as two grams a day without fear of any untoward cumulative effects.

Salicylic acid and its derivatives—salol, salophen, salipyrin, and aspirin—are often classed with antipyretics. Salicylate of soda lowers the temperature in cases of rheumatic polyarthritis, but it is the specific of this infection. On the other hand, it is without effect in infectious pseudorheumatism. It may, therefore, serve the purposes of differential diagnosis.

Salicylate of soda and salol owe certain antipyretic virtues to their antiseptic properties. Hence, these medicines may be employed to combat certain symptomatic fevers, notably those related to suppurations of the biliary passages or the urinary apparatus. In these cases, however, the process is not a truly febrifuge action. The medicine produces its effect by acting upon the cause. Its administration is, therefore, clearly indicated and realizes an etiological medication.

Finally, by a mechanism as yet illy elucidated, guaiacol when applied to the skin has the interesting property of lowering the temperature. It acts so powerfully that, if precautions are not taken, collapse may occur. This method is available particularly in the treatment of tubercular fever.

Conclusion. From the foregoing brief study we may conclude that there are no good antipyretic medicines. At all events, the dangers and inconveniences of fever have been much exaggerated. In many cases to arrest the febrile process would be to harm the patient.

The true antipyretic is that which suppresses fever, not by disturbing the reactionary movement of the organism, but by acting upon the cause of the febrile process. This is precisely what is realized by specifics—quinine in malaria, mercury and iodides in syphilitic fever, sodium salicylate in rheumatism, the insoluble antiseptics in fevers of intestinal origin, and antiseptics or antitoxins introduced into infected foci. These are substances which deserve to be considered as antipyretics of predilection. They act by combating the cause of the morbid process, while most of the febrifuges, by modifying the reactionary mechanism, hinder nature's work. Balneotherapy alone represents a natural medication, for it simply favors dissipation of heat, which is already increased by the disease. At the same time baths act upon the principal apparatus of the economy. Hence, they are now currently used and are applicable to a great

number of infections. Being given lukewarm or cold, according to circumstances, the bath is the only true antipyretic that may be prescribed.

Venesection.

We are far from the epoch when blood-letting was systematically practised in fevers, when it was imagined that acute diseases could be checked by repeated abstraction of the vital fluid. At present this method is seldom resorted to in the treatment of infectious diseases. It is employed only in pneumonia or in certain complications. We must, therefore, briefly study its influence upon the organism and its possible indications in infections. Without presenting the history of the physiological effects of blood-letting, which is still obscure on certain points, it will suffice to refer to the acquired results. An easily foreseen first effect is a reduction in blood pressure. This phenomenon is produced as soon as the vein is open. Tension rapidly decreases, to again rise slowly when the flow is arrested, and returns to a figure somewhat below that observed at the beginning. In this respect successive blood-lettings act less and less energetically. Coincidently, according to Marey's law, the pulse becomes more rapid and weak. If, however, arterial tension is very considerable and venous stasis very marked, the pulse becomes fuller. The red blood corpuscles diminish in number, but this first phenomenon is followed by a very marked increase in the hematoblasts. This second result, noted by Dr. Hayem, is in perfect harmony with the researches which have been pursued on the hematopoietic organs, demonstrating their increased functional activity. After the bleeding the cells proliferate in order to repair the losses of the organism, and, as always, compensation exceeds the primary effect. The slight leucocytosis which supervenes in most cases is probably produced by the same mechanism. The diminution of the blood mass has two important consequences: it facilitates the circulation in parts which are overloaded with blood and relieves passive congestions, with the result that the functions of the organs are better fulfilled. The effect is particularly appreciable in the lungs. At the same time, an osmotic current is established from the tissues toward the bloodvessels. The interstitial fluids pass into the circulation. If they are toxic, their action upon the organism may be dreaded, and, in fact, Lisfranc rejected blood-letting whenever a purulent or putrid focus existed. If, however, elimination is easy, blood-letting favors the passage into

the blood of substances deposited in the interstitial plasma, and thus promotes disintoxication of the organism. Blood-letting acts the better the easier the work of the heart is rendered under its influence, and, consequently, the urinary secretion is increased. As a matter of fact, experiments have demonstrated that diuresis is increased in consequence of blood-letting. Since we are speaking of poisons, it is well to remark that blood-letting is one of the best means for freeing the organism from them. With good reason, Prof. Bouchard has laid stress on this point. He notes that a blood-letting of 32 grams eliminates from the organism 0.5 gram of extractive matters. In twenty-four hours the urine eliminates 8 grams of such matters. This small loss of blood thus throws out of the body the one-sixteenth part of the poison accumulating in one day when urinary secretion is suspended. This result seems still greater when it is remembered that 280 grams of intestinal fluid or 10 quarts (9 litres) of sweat are required in order to produce the same effect.

By modifying blood pressure, blood-letting is followed by dilatation of the capillaries and, consequently, a more active irrigation of the tissues. The result is a favorable modification in nutrition. In fact, the urine of twenty-four hours eliminates more urea, more phosphoric acid and extractive matters (Lépine). The same influence may be found by studying the organic apparatus; the nervous system becomes more active, and respiration easier and deeper. A last effect of blood-letting is a modification in the temperature. Under its influence temperature is lowered, and this effect is the more marked as calorification is increased. The thermometer has sometimes marked one or two degrees less after blood-letting. Unless, however, abundant and repeated bleedings are practised, the effect is transitory; the temperature soon rises, and at times exceeds the former degree.

Let us now apply these data to infectious diseases. The indications may be formulated in the following manner: Blood-letting is indicated for combating excessive hyperthermia. Congestion in the venous system embarrasses cardiac contraction and gives rise to passive congestion in the lungs, kidneys, and brain. The result is a profound and rapid intoxication of the organism, especially if renal insufficiency coexists.

Blood-letting is contraindicated, even under the foregoing conditions, in children, the aged, and debilitated individuals. In other words, the advisability of blood-letting is to be considered only as

regards vigorous adults, especially those presenting what the ancients designated under the term plethoric temperament.

Let us now consider a determined infection, the only one, perhaps, in which blood-letting is still quite frequently employed—*i. e.*, pneumonia. Formerly, blood-letting was resorted to systematically. Tommasini, of Bologne, practised as many as twenty blood-lettings of from 400 grams to 500 grams each. He thus drew ten quarts (nine litres) of blood. Broussais and Bouillaud followed an analogous method. At present there is general agreement that blood-letting does not check pneumonia; it does not even abridge its course, but it improves certain symptoms. It is indicated in all vigorous adults in whom fever is intense and dyspnea is troublesome and in whom an extensive focus surrounded by a vast zone of hyperemia and edema is found. It is likewise indicated when the patient is cyanosed and the right heart is dilated; also when venous stasis affects the brain, giving rise to somnolence or a semicomatose state. In this case, blood-letting brings immediate relief; respiration becomes freer, deeper, and shorter; the pulse is strengthened, the nervous disturbances diminish, and in several cases an amelioration in cardiac manifestations and increased diuresis are clearly observed.

Blood-letting has been practised in all infectious diseases. Typhoid fever, eruptive fevers, erysipelas, inflammations of the serous membranes, and especially acute articular rheumatism have been treated by blood-letting. Dr. Du Castel thinks that this method may render service in variola when very marked phenomena of cerebral stasis are present. This particular case excepted, blood-letting is indicated in infectious diseases when intense pulmonary and renal disturbances are observed. It may likewise be available in other localizations in the viscera or serous membranes. In this case, however, local depletions and wet cuppings are mostly employed.

Blood-letting is, therefore, reserved for those cases in which intense pulmonary congestion hinders hematosis and embarrasses the function of the right heart. It becomes altogether urgent in cases of acute pulmonary edema. In certain fever cases, especially when renal lesions are present, pulmonary edema may rapidly appear and, at times, cause death within a few minutes. This dangerous manifestation is observed particularly during convalescence in the course of scarlatinal nephritis. This is one of the most formal indications for blood-letting, as the procedure gives marvellous results against this visceral manifestation.

When the renal lesion influences the nervous system the indication for blood-letting is not any less clear. It is likewise during convalescence from scarlatina that uremic accidents involving the brain are observed and command bleeding. While this method is serviceable against the symptoms of chronic nephritis, it is particularly indicated in acute nephrites which manifest a natural tendency toward recovery. It suffices to assist the organism a little in order to avoid grave manifestations.

The knowledge of the rôle played by intoxication in the production of infectious symptoms leads to the question whether it would not be advisable to practise blood-letting in certain grave cases. The amount of poisons impregnating the economy would thus be diminished. The suggestion is evidently rational. It may, however, be objected that the loss of blood would weaken the patient. The question is again laid before us to-day. We know, in fact, the marvellous results of salt-water injections in the treatment of infections. Some authorities have, therefore, proposed to combine the two methods. The idea is perfectly reasonable, and the disadvantages of venesection are thus offset by saline infusion.

Injections of Artificial Serum.

Intravenous or subcutaneous injections of artificial serum are daily employed at present in the treatment of the most varied infections. While there is general agreement as to their usefulness, their mode of action is still a subject of controversy. Drs. Dastre and Loye, who were the first to transfer the question to experimental ground, suppose that salt-water injections realize lavage of the organism. It has been objected, however, that in hydremic animals the renal secretion is profoundly modified. The urine is an aqueous fluid which, in certain cases, carried less extractive matters than it would under normal conditions. Some experimental investigations have confirmed this conclusion by demonstrating that infected or intoxicated animals upon which lavage of the blood is practised die before the controls. It is to be noted that the problem is far more complex than seems at first view. When salt-water is injected beneath the skin or into the veins quite different effects are produced. The amount of fluid contained in the vessels is modified. Contrary to what might be expected, the blood pressure varies little, at least if it was normal. We must, therefore, presume that either vasomotor modifications or some eliminations have rapidly

taken place. In the latter instance, if a portion of the fluid is rejected by the emunctories, another portion is deposited in certain tissues, and modifies the nutrition of the organism, and consequently produces changes in the activity of various parts. As a matter of fact, experiments have demonstrated that the responsive aptitude of the nervous system is considerably increased. This modification is immediate; it supervenes immediately after the injection. At the same time, however, the nutritional modifications are followed by changes in the histological structure of certain tissues. This is readily recognized by studying the bone-marrow.

Influence of Injections of Artificial Serum upon Absorption. The first question is whether injections of salt-water modify the absorption of poisons deposited beneath the skin or in the alimentary canal. Magendie took up this problem. He introduced a poison into the pleura after having practised blood-letting. The disturbances were manifest at the end of thirty seconds, while in an intact animal they did not appear until two minutes after. On the other hand, when he injected one or two quarts (litres) of water into the veins the symptoms were then more tardy; they often did not appear when two quarts were introduced. When, however, blood-letting was practised upon this hydremic animal the toxic manifestations developed as the blood was flowing. The experiments of Delbet likewise established that intravenous injections of salt water prevent the absorption of strychnine introduced into the peritoneum. More recent experiments pursued by Dr. Chassevant also demonstrated that such injections retard and attenuate the action of strychnine introduced beneath the skin. Taking up this question, I learned that salt-water effectively retards the absorption of strychnine. The fluid was injected into rabbits by the intravenous route, at a temperature of 102.2° F. (39° C.), in amounts of 3 to 4 c.cm. per minute per kilogram of animal. The amount introduced varied from 3 to 228 c.cm. per kilogram. Five minutes after the salt-water injection the animals received subcutaneously from $\frac{1}{2}$ to 2 mg. of strychnine sulphate. The injections of salt-water in doses of 3 to 70 c.cm. per kilogram did not greatly modify the resistance of the animals; at times they increased it, and at other times they diminished it. When, however, considerable quantities were introduced, that is from 166 to 228 c.cm. per kilogram, the symptoms were delayed and less marked. Thus, 1 mg. killed a rabbit within eighteen to thirty-one minutes; while it takes half an hour to kill

an animal having previously received 210 c.cm. of salt-water per kilogram. By diminishing the dose of the poison we observed no disorder whatever. In one rabbit 7 mg. produced no disturbance, not even an exaggeration of the reflexes, while two other rabbits which received the same amount of strychnine per kilogram, had intermittent convulsions extending over a period of seven or eight minutes; then the animals recovered, although for thirty to forty minutes they retained a very marked exaggeration of the reflexes.

When strychnine is injected into the veins instead of beneath the skin, the results are different. The animals which received salt-water reacted far more rapidly and energetically, and died before the controls. This result demonstrates that injections of salt-water, while retarding the action of strychnine injected beneath the skin, do not act by diminishing the sensibility of the animals. It must, therefore, be admitted either that they hasten elimination or that they hinder absorption. By injecting strychnine into the veins at a very slow rate, so as to introduce the convulsifying dose in an hour and a half, elimination should be effected still more easily than is the case in subcutaneous injections. The animals should not present any disorder. Experiments having given the contrary result, I concluded that the rôle of elimination is insignificant. Injection of large quantities of salt-water into the veins retard and diminish strychnine intoxication because they hinder absorption.

Here, therefore, is a first result which must be taken into account for therapeutic indications. The result should not, however, be generalized. What is true of alkaloids is not applicable to microbic toxins. Enriquez and Hallion demonstrated that previous injections of salt-water in nowise prevent the absorption of diphtheritic toxins injected beneath the skin.

Influence of Injections of Artificial Serum upon Elimination. What is the influence of intravenous injections upon renal elimination? Numerous researches have been pursued on this subject. Dastre and Loye, who have well studied the method from an experimental standpoint, practised lavage of the blood. The attempts, however, which were made to save the intoxicated or infected animals generally gave no results. The animals thus treated died more rapidly than the controls. By studying the urine of animals having received such amounts of salt-water as to double the blood mass, Carrion and Hallion learned that while the amount of water excreted increases, the amount of matters eliminated, except that of

sodium chloride, is smaller than normal. Sodium chloride is substituted in the urine for other materials; it does not carry them away. These results account for the failure of attempts of experimental therapeutics.

These results, however, should not be hastily generalized. As a matter of fact, I have obtained different results by studying the elimination of two substances which are easily detected in the urine —ferrocyanide of potassium and sulphindigotate of soda.

In a first series of experiments, rabbits received through a vein of the ear 4 c.cm. of a 1: 200 solution (2 centigrams) of ferrocyanide of potassium. The injection lasted a minute. Then an effort was made to discover at what moment the urine gave the characteristic blue color with perchloride of iron. In order to determine this, we collected every minute a few drops of the urine either by means of a catheter or by compressing the bladder through the abdominal wall. By experimenting upon six normal rabbits we discovered the presence of ferrocyanide in the urine at the end of ten, eleven, thirteen, fourteen, sixteen, and seventeen minutes—*i. e.*, thirteen minutes on an average. In four rabbits into which we injected salt-water before the introduction of the ferrocyanide we obtained the following figures: seven minutes in a first rabbit having previously received 62 c.cm. of salt-water per kilogram; six minutes in a second rabbit having received 100 c.cm.; eight minutes in two others, one having received 133 and the other 160 c.cm. per kilogram: the average is seven minutes. The differences are, therefore, very clear. The previous injection of salt-water caused the ferrocyanide to appear in the urine twice as rapidly as in the controls.

It is very difficult to determine at the end of what time elimination is completed, for the ferrocyanide diminishes little by little, and a moment arrives when reaction with perchloride of iron becomes extremely doubtful. Nevertheless, here are figures presenting a comparative value. In three normal rabbits reaction discontinued respectively at the end of four hours, four hours and forty minutes, and five hours. In three rabbits which received salt-water after the injection of the ferrocyanide reaction ceased: in the first one, which had received 62 c.cm. per kilogram, at the end of four hours; in the other two, which had received each 100 c.cm. at the end of three hours and forty minutes and three hours and thirty minutes, respectively. Thus, it may be stated that, on an average, elimination lasts four hours and thirty-three minutes in the controls, and

three hours and forty-three minutes in the injected animals. The differences are appreciable, but not important.

Clearer results may be obtained by the employment of sulphindigotate of sodium. When 2 c.cm. of a 3 per cent. solution of this substance is injected into the veins of a rabbit, at the end of three or four minutes a urine of a decidedly blue color begins to flow. The passage of the coloring substance is, therefore, effected far too rapidly to permit the experimenter to notice differences in hydremic animals. Hence, I simply sought to learn whether, by injecting salt-water after the introduction of indigo, I favored the elimination of this coloring matter. The results were similar to those obtained with ferrocyanide: the urine recovered its normal aspect at the end of four hours and a half in the controls, and at the end of three hours and a half to three hours and fifteen minutes in the treated animals. It is understood that in all these experiments the varying degrees of dilution of the excreted fluid were always taken into account.

In order to obtain a more convincing demonstration of the influence exercised by injections of salt-water, I introduced into the veins 15 to 20 c.cm. per kilogram of a 3 per cent. solution of sulphindigotate of soda. The animals soon presented a bluish color, fairly appreciable in the nose, lips, gums, nictitating membrane, and conjunctiva. On cutting off the fur the skin was found to be of a deep blue color. Preserving one animal as control, I injected salt-water into the other. An injection of 130 c.cm. per kilogram notably accelerated the return of the normal color, especially in the mucous membranes. At the end of an hour and a half, for example, the buccal, nasal, and ocular mucous membranes became grayish; at the end of two hours or two hours and a half they recovered their normal hue. At this moment, in the control animals the same parts were still of a slightly greenish-blue. The differences were analogous with regard to the skin, but they were less marked. With the controls as well as with the treated animals, decolorization was effected far more slowly in the skin than in the mucous membranes. The results were the same in the viscera. On sacrificing the animals at different moments I noticed that decolorization was more rapidly produced in those which had received salt-water injections. For example, at the end of three hours the liver had resumed its normal aspect, while it was still blue in the controls. The kidneys remained colored for a longer time, but their color

was less marked. Lastly, at the end of seven hours, the animals treated presented very little, if any, abnormal color; while the kidneys and the tendons of the controls were still blue.

It may, therefore, be concluded that intravenous injections of salt-water truly realize lavage of the blood or rather of the organism; they hasten the appearance of ferrocyanide of potassium in the urine and accelerate its elimination. Finally, as our experiments with indigo demonstrated, they promote elimination of noxious substances deposited in the tissues.

It would be worth while to take up the study of the question by varying the doses and employing the most varied substances. It would thus be possible to establish the laws of elimination. All that we can say at present is that injections of artificial serum seem to produce divers effects according to the substances employed. They favor elimination of some and hinder that of others.

Influence of Injections of Artificial Serum upon the Functions and Nutrition of the Organism. The study of strychnine intoxication enabled me to recognize that injections of artificial serum modified the responsive aptitudes of the organism. In order to avoid errors arising from modifications in absorption, it is necessary to introduce the poison directly into the veins. The results were extremely clear. By injecting into the veins doses of strychnine which produced no disturbance in the controls, I caused fatal convulsions in the hydremic animals. In several of my experiments the injections were made very slowly. I thus hoped to allow time for renal elimination to take place; but no matter whether the rate of the injections was rapid or slow, the result was the same. The conclusion is, therefore, that salt-water injections increased reflex excitability; the employment of strychnine was designed to determine the sensibility of the spinal cord. The concordant results obtained demonstrate that saline infusion produces a dynamogeny in the nervous centres. This therapeutic method is, therefore, indicated in all cases of depression or asthenia. Clinical experience shows that this deduction is well founded.

Another point on which clinical observation and experimentation are agreed is the influence exercised upon the blood pressure. In certain cases pressure rises by a very simple mechanism. For example, in the case of an individual in whom the arterial pulsation is no longer appreciable, and death seems to be imminent as the result of profuse hemorrhage, injection of salt-water into the veins

revives the patient immediately; the cardiac pulsations are strengthened, and the pulse improves. On the other hand, it may be supposed that the injections also act upon the nervous centres and that they indirectly raise blood pressure. This action may account for the results obtained in the treatment of infections of the digestive canal, such as cholera, enteritis, and infections of the peritoneum. It is precisely in such cases that the blood pressure falls to the minimum. Bosc and Vedel demonstrated the good results of saline injections in animals which were inoculated with the colon bacillus. On the other hand, Enriquez and Hallion followed the variations of blood pressure in animals at the last stage of diphtheritic intoxication. Under the influence of the injections the blood pressure, which had been very low, was seen to rise progressively, while the various symptoms improved. Amelioration was not, however, permanent. This was probably due to the fact that experimental intoxication was too brutal, and the animals could not be saved.

The nervous and circulatory functions as well as all the tissues of the organism are favorably influenced by injections of salt-water. L. Garnier and Lambert demonstrated that the muscles consumed more oxygen and eliminated more carbonic acid. This modification seems to be quite independent of any nervous influence, since it was observed in the muscles separated from the body of the animal. The same authors have likewise discovered that the amount of glycogen diminished in the liver, not because it was eliminated, but simply because the hepatic cells had become more active and consumed it more rapidly. Chemical analysis thus agrees with experimentation and clinical observation to establish that artificial serum is a powerful stimulant of nutritional activity and that it possesses a high dynamogenic power. Histological investigations prove the same thing. To be convinced of this, it suffices to examine the bone-marrow of animals submitted to this medication. I recognized, with Dr. Josué, that fat was rapidly absorbed and the cells of the marrow proliferated. This fact presents certain interest from the standpoint of pathological physiology, since it is known that bone-marrow, by furnishing round cells to the blood, plays an important rôle in the defense of the organism against infections.

Indications of Injections of Artificial Serum. The first attempts were made as early as 1831. Joeniken, of Moscow, injected slightly acidulated water into a cholera patient at the point of death. The patient died two hours later. A Scotch physician, Latta, in 1832,

advocated intravenous injections of salt-water in cholera. In 1850 Zimmermann treated by this method a certain number of cholera patients, and reported thirty cures. Lorain, in 1866, and Dujardin-Beaumetz, in 1876, reported other facts. These first attempts did not, however, have followers, and we must turn to the contributions of Hayem to see intravenous injections or artificial serum take an important place in therapeutics.

Subcutaneous or intravenous injections of salt-water are at present employed in the treatment of the most varied infections. The quality of fluid to be injected has been varied. On the basis of highly interesting theoretical considerations, Quinton has recently proposed to employ diluted sea-water. This liquid is said to be better borne and to exercise a more energetic therapeutic action.

In our wards we employ either 8 per 1000 solutions of salt-water or Hayem's serum, which, as is known, contains 5 grams of NaCl and 10 grams of Na_2SO_4 per litre (quart). The liquid is sterilized and introduced after being heated to 104° F. (40° C.). Dawborn employed solutions heated to 120.2° F. (49° C.). While the experiments of Richet, Langlois, and Athanasiu demonstrated that injections of hot water are well borne by animals, those of Lepine and ours show, on the other hand, that ice-water does not produce any disturbance. It may be concluded that the body heat may be modified by injections of more or less heated fluids. For the time being, it seems more prudent to employ solutions the temperature of which is near that of the body. This precaution is indispensable when an intravenous injection is practised. It is less important in subcutaneous injections. When it is necessary to act promptly, intravenous injection is preferable. If, however, the vein cannot be discovered, for example, in an obese individual or in a patient whose bloodvessels have contracted, intraperitoneal injection may be practised. According to experiments pursued on animals, this method is harmless and has the advantage of permitting very rapid absorption. When there is no urgency the fluid may be injected into the rectum, after having given an evacuative enema.

Whatever the route of introduction, injections produce identical effects, appreciable especially in the case of intravenous injections. Bosc, Vedel, and Michaux have described the various manifestations observed under these circumstances. During the injection, the pulse becomes slower, more regular and stronger. The central and axillary temperatures slightly rise; sometimes diarrhea is produced.

Immediately after the injection, the patient experiences a feeling of quiet exhilaration which lasts from thirty minutes to an hour. Then violent chills supervene; the extremities become cold and blue; the pulse and respiration are accelerated, and the reflexes exaggerated. The temperature rapidly rises. The patient then experiences a sensation of heat. This second stage is followed by a more or less rapid return to the normal. In certain instances fever disappears completely and in a definitive manner. Owing to the violent reaction thus produced, the organism seems to have arrested the morbid evolution.

After subcutaneous injections similar reactions occur, but they are more tardy and less intense. Intravenous injection is indicated particularly in very acute infections and in diseases aggravated by a sudden complication. Cholera and choleriform diarrheas belong to the first instance; peritoneal infections, supervening in consequence of a surgical operation or in the course of an infection, may likewise be treated by this method. In cases of peritonitis, a reduction in arterial pressure is not infrequently the first symptom observed. An intravenous injection raises the blood pressure, and thereby stimulates activity of the glands and assures diuresis. The results of intravenous injections are often, however, of a transitory character. It is then necessary to repeat the injection of the fluid. If one litre is injected, four or five similar injections may be given in twenty-four hours. In one case Lejars introduced seven litres in seven hours. In another instance he injected twenty-six litres in nine days.

Very satisfactory results may also be obtained by combining subcutaneous and intravenous injections. Owing to their immediate, almost instantaneous, effects the latter palliate the early symptoms. The introduction of salt-water beneath the skin furnishes to the economy a provision of fluid which passes slowly into the blood as the emunctories eliminate the water introduced. In infections with a slow course, in adynamic fevers, and in cases of myocarditis subcutaneous injections are usually employed. Finally, when a profound intoxication of the organism is suspected, blood-letting and transfusion may be combined. Everyone knows of this method proposed by Dr. Barré: 150 to 300 c.cm. of blood are taken from a vein, and from 200 to 1200 c.cm. of salt-water are then injected into the veins or beneath the skin.

The amount of the fluid injected varies considerably according to

the individual under treatment, the disease observed, and the end pursued. In grave cases, from 500 c.cm. to 1000 c.cm. of artificial serum are introduced into the veins. In most cases the author employs subcutaneous injections. The amount varies according to the age of the subject and the nature and gravity of the case. In children about two years of age, from 10 c.cm. to 20 c.cm. suffice. The author generally injects from 200 c.cm. to 300 c.cm. in the case of adults. If the case is more serious, from 400 c.cm. to 500 c.cm. may be used. Moreover, in case of need, subcutaneous injections may be repeated several times a day, and it is surprising to see with what facility patients bear them.

All sorts of infections may be treated by this method. It is employed in all grave pyrexias, notably in those in which the nervous system is extremely weakened and there is tendency to adynamia and cardiac collapse, a dehydration of the organism expressed by the dryness of the mucous membranes and of the skin, a diminution in the amount of urine, and the occurrence of profuse and multiple hemorrhages.

The existence of pulmonary, renal, or cardiac complications is at times considered a contraindication. Lesions of the lungs, the author thinks, contraindicate intravenous injections, but they should in no-wise prevent subcutaneous injections. He often prescribes artificial serum for children suffering from bronchopneumonia, provided, however, that small amounts be given two or three times a day. The same rule should be followed in the case of renal or cardiac complications. Experience has demonstrated that intravenous injections are often harmful, and if a lesion of the heart is present, this may cause sudden death. On the contrary, subcutaneous injections are well borne. The method is available not only during the stationary period, but at the end and during convalescence from infections. The author has resorted to it several times when recovery was not clearly established, notably at the end of typhoid fever. An injection of 100 c.cm. often suffices to cause the last symptoms to disappear. During convalescence from infections, when the patient is not restored to health with gratifying rapidity, recourse may be had to injections of small amounts of saline solutions, following the advice of Landouzy. From 10 c.cm. to 20 c.cm. of artificial serum are introduced beneath the skin twice a week. This is a method which renders most appreciable service in the case of tedious convalescence.

Special Indications for Injections of Artificial Serum. After the general study which we have presented concerning saline injections, we shall be very brief on particular indications.

Numerous cases of surgical, obstetrical, and medical septicemias have been successfully treated by this method. Intravenous injections have mostly been employed. Tuffier reported two cases of tetanus cured by saline injections preceded by blood-letting. The attempts made in hydrophobia by Magendie, Oré, and Reclus were negative. Among medical affections, digestive infections particularly are best treated by this method. Cholera is the disease which is most frequently treated by intravenous injections. In order to succeed, it is necessary, as has been shown by Hayem, to intervene early, as soon as the pulse shows weakness, and not, as is often done, in the period of collapse. From 1500 c.cm. to 2000 c.cm. and even 2500 c.cm. are injected into the veins. If the symptoms return, the injection is repeated on the following day. In certain instances recovery has been obtained only after five or six intravenous injections. As has already been stated, there is advantage in injecting at the same time 400 c.cm. to 500 c.cm. beneath the skin. In mild cases the subcutaneous method exclusively is used. Finally, excellent results are obtained by prescribing coincidently warm baths so as to maintain the temperature of the body and avoid return of the algid state. The same rules are applicable to choleriform enterites. The indications are the same; the less grave the symptoms the more sufficient the hypodermic method generally proves to be. Treatment is likewise identical in cases of gastroenterites of the newborn and cholera infantum. Marfan advises, with good reason, the addition of a small amount of caffein to the fluid: 75 cg. of citrate or benzoate of caffein are added to 300 c.cm. of salt-water, and three injections of 5 c.cm. to 20 c.cm. daily are given.

Typhoid fever, especially its adynamic forms, is favorably influenced by the injections. In the case of intestinal hemorrhage, the effects of the injections are very remarkable. In order to be convinced of this, it suffices to bleed an animal. At the moment at which death seems to be imminent an intravenous injection is practised, and immediately the heart beats with energy and all the disturbances disappear. In mild cases saline injection beneath the skin, and, if the symptoms are alarming, into the veins, is the preferable treatment. By this method patients who had already fallen into a state of collapse have been cured. The second important complica-

tion—*i. e.*, perforation of the intestine—likewise requires a saline injection, which renews the forces of the patient and enables him to bear surgical intervention.

Among other infections, typhus fever, typhoidal affections, notably ulcerating endocarditis and adynamic pneumonia, must be treated by subcutaneous injections. The author employs them also in eruptive fevers, at least in grave forms, and in erysipelas. When the manifestations persist and the temperature remains high in spite of cold baths, subcutaneous injection often suffices to bring about defervescence. In several cases, after having introduced 300 c.cm. to 400 c.cm. beneath the skin, the symptoms disappeared within twenty-four hours. This method may be employed even in cases of wandering erysipelas. It is then necessary to inject the fluid into a part of the organism far from the diseased spot.

To sum up, barring a few particular cases, which we have indicated above, saline injections represent one of the best methods of treatment of infectious diseases. They succeed far better in man than in animals, probably for the reason that the nervous system in man is far more profoundly affected. By stimulating its activity, the injection favors general nutrition and the functions of the principal organs. Moreover, it perhaps acts also by furnishing water to the organism. We have several times referred to the importance of water for the activity of the cells, and if it is true that in the fight against infections, the organism tends to return to a functional state characteristic of a younger age, the chemical formula of this tendency is an increased amount of water. This is a new reason, based upon numerous analyses, for having recourse to injections of salt-water.

Symptomatic Medication.

In a great number of cases the physician must combat certain symptoms or complications regardless of the mechanism governing their development. It is then a question of dangerous or painful disorders, which are about the same in all infections, and require a common therapeutics. Among these disorders several have already been studied, and we shall only briefly recall their indication. Of others we shall speak at some length.

Treatment of Febrile Manifestations. We have sufficiently indicated the rules that must guide us in the treatment of fever and have shown that the only rational medication is represented by cold or lukewarm baths. In cases in which fever starts with chills and in

those in whom chills occur in the course of a pyretic infection, the patient must be mechanically heated. As has already been stated, chills represent a reaction of the organism calculated to raise the temperature in order to combat the hypothermizing action of toxins. At this moment the skin is cold and pale, owing to contraction of the small peripheral arteries. Since the investigations of Marey it is known that when the skin is cold it means that the individual tends to become heated, and that when the skin is warm he tends to become cold. This formula, paradoxical in appearance, is, nevertheless, very simple. When the skin is cold, dissipation of heat is reduced as much as possible; this dissipation increases as the cutaneous temperature rises. When, therefore, the skin of an individual is cold, heat must be furnished, and when the skin is warm heat must be abstracted. In both instances naturalistic medication is practised. Consequently, during chills the patient must be well covered, and hot water bottles should be placed in his bed. Moreover, to the same end, hot beverages must be given. This medication is a popular one. Mistaking the effect for the cause, many persons think that the initial chills, notably in influenza, represent a cold which causes the disease, and flatter themselves as to their ability to arrest the evolution by means of hot applications and beverages. The effect is real, but the interpretation is erroneous. The truth is that it is not the chill that is combated, but the organism is assisted in warming itself.

At the end and at times during the course of fevers, sweating is not rare. It commonly appears at the end of a paroxysm after the period of heat. Sweating requires some hygienic precautions. The perspiration should not be allowed to grow cold upon the skin. The bed-clothes should, therefore, be changed, dry friction practised, and the patient covered with blankets. Finally, as sweating gives rise to thirst, the patient must be given drink; hot beverages and infusions should be administered. The sweating of cachectic and tubercular patients requires special treatment. Five milligrams of agaricin and two to five grams of camphoric acid may be prescribed. The best medicine, however, is, without doubt, the neutral sulphate of atropin. One-half milligram granules are first given, and if this dose proves to be insufficient, two, three, and even four of them may be administered in a day. Sweating must be combated, particularly during the night, as, by its abundance, it disturbs the sleep of the patients. The author has sometimes observed night-sweats during

convalescence from acute infections. A granule of atropin given three or four evenings in succession suffices to make them disappear.

In infections which terminate by crisis, notably in pneumonia, the temperature may suddenly fall below the normal. This disturbance is transitory in adults, but in children, and especially in the aged, hypothermia may be excessive and attended by alarming phenomena of collapse. Hot baths, hot water bottles, cutaneous friction, and stimulating medicines must then be prescribed.

Treatment of Nervous Manifestations. The general treatment of nervous disturbances, whether the case is one of excessive excitation or depression, consists in lukewarm or cold baths. This is the best procedure for regulating the nervous functions, remedying delirium, and inducing sleep. It is likewise the treatment for that frequent and alarming symptom observed in children—*i. e.*, convulsions. These are not rare at the beginning of infections. Convulsions are the equivalent of chills in adults. Commonly transitory, they require no special treatment. A few hygienic rules suffice. Most parents, frightened at seeing their children suffering from convulsions, have the deplorable habit of taking them in their arms, slapping them on the back, and walking the floor with them. On the contrary, they should be kept at rest. The child should be placed in a large bed so as to avoid the danger of falling out when agitated. The room should be kept in semidarkness and free from noise. When convulsions are repeated they indicate a lesion in the nervous centres or a too great excitability of the child. In the latter case they are the equivalent of delirium. It is then necessary to resort to lukewarm baths at 100.5° F. (38° C.) during the intervals of convulsion, or, if fever is intense, to baths gradually rendered cold so as to reach a temperature of 89.5° or even 86° F. (32° or 30° C.). For the same purpose antispasmodic preparations may be employed, among which the most usual are the tinctures of musk, asafetida, and valerian, which are prescribed in doses of ten to thirty drops, according to the age of the children. In the case of gastric intolerance, a musk enema is generally given.

The treatment of delirium requires special consideration. Balneotherapy takes the first rank. In young and robust adults cold baths are given. In children and persons above forty years of age, lukewarm baths are administered. It is well to note, however, that in these cases cold effusions should be practised upon the head during the bathing. If the patient is much agitated, for instance, in the

case of alcoholic delirium, an additional difficulty faces us. After having been brought back to his bed, the patient may attempt to get out and, even when constantly watched, he may at times succeed in rising. It is then necessary to force him to lie down again. In hospitals the difficulties are still greater, and physicians are sometimes compelled to resort to coercive measures. One of the best methods, which, however, is applicable only to mild cases, consists in placing on each side of the bed a plank so as to prevent an easy escape. When delirium is more intense it is necessary to bind the patient, but in such a manner as to allow him to move easily in the bed.

The therapeutic indications vary according to the cases under treatment. There is a neuropathic delirium related to a previous state of the individual, and there is a delirium dependent upon chronic intoxications, notably alcoholism. Neuropathic delirium, when not very intense, requires no special therapeutics. Balneotherapy is sufficient. When intense, delirium must be treated by means of antispasmodics. Bromides may render service. In infectious diseases, which are so often attended by cardiac or renal disturbances, it is well, in general, to avoid potassium salts. Bromide of sodium should be given in doses of from two to four grams a day. Musk is also available, but the medicine to which the author resorts most frequently is valerian. The best preparation is the extract, of which 4 to 6 grams are given a day. An infusion of the root is also useful, 15 to 30 grams of which may be given as an enema, or a 10:1000 infusion of half an hour. Valerian acts mostly by the isomeric carbohydrate of turpentine oil, which it contains, and not by valerianic acid. The author, therefore, avoids the use of valerianate of ammonia.

In alcoholic delirium occurring in the course of an infectious disease, the extract of valerian may be employed. The true medication, however, is alcohol associated or not with opium. In our hospitals Todd's potion is usually prescribed. The French *Codex* formulates it in the following manner: old brandy or rum, 40 grams; simple syrup, 30 grams; tincture of cinnamon, 5 grams; distilled water, 75 grams.

As brandy and rum contain 45 to 60 per cent. of alcohol, the amount given above is too small. In fact, Todd prescribed from 100 grams to 150 grams of brandy in twenty-four hours for cases of medium severity, and from 300 to 500 grams in grave cases. The

second indication, however, formulated by Todd, and which is perhaps the most important but is often overlooked, is that the alcoholic potion is not to be given in very large doses. According to this famous clinician, 14 grams of brandy should be given every two hours. If this precept is not followed, grave accidents may be produced by the use of this alcoholic beverage. A very simple procedure consists in giving a dessertspoonful of rum with two or three times its volume of sweetened water every two hours. If the agitation is extremely violent, alcohol may be associated with opium. This association is frequently indicated in pneumonia, erysipelas, and variola. From 5 cg. to 10 cg. of extract of opium or from 20 to 40 drops of Sydenham's laudanum is given in twenty-four hours. The opium preparations are likewise to be given in fractional doses. The desired quantity may be given in Todd's potion or with wine. Wine to which the daily dose of laudanum is added has a very remarkable action; one litre of such wine may be given in twenty-four hours. If there is tendency toward adynamia, champagne is to be preferred. The treatment must be completed by certain medicines calculated to combat cardiac disorders which are so frequent in such cases. Spartein and strychnine may be administered subcutaneously. One cubic centimetre of a solution containing 5 cg. of sulphate of spartein and 1 mg. of sulphate of strychnine may be injected morning and evening.

This treatment would be perfect if the cerebral disorders of alcoholic patients did not frequently coexist with renal lesions. Albuminuria absolutely contraindicates the employment of alcohol and of opium, which then produce extremely grave phenomena of depression. Baths, bromides, and valerian will suffice in such cases. Moreover, let us recall that, in certain cases, delirium may be cured by specific medication. Quinine should be given in the case of malarial delirium and mercury and iodides to syphilitics.

When the nervous system is much excited insomnia is frequent. This disturbance is combated by the medications directed against delirium and by the general therapeutics of infection. If, notwithstanding the baths, insomnia should persist, hypnotics must be employed. As the patients soon become accustomed to their action, it is well to change the medicine as soon as its effect is exhausted. One gram of sulphonal, of trional, or of hypnal, 2 grams of chloral hydrate, or a mixture of chloral and bromide of sodium, in the dose of 1 gram of each, may be administered. Opium should be mis-

trusted. It is indicated only in alcoholic patients and in the course of variola. Even in these cases, however, it is to be avoided if there is albumin in the urine or the secretion is too scanty. In children lukewarm baths almost always suffice. In case of need a little bromide of sodium or calcium may also be prescribed; 20 cg. or 25 cg. for each year of the age may be administered.

When the nervous system seems to be exhausted, diffusible stimulants are to be resorted to. Potions containing rum or brandy, champagne, and vinous beverages may be prescribed. Wine may be given to children; 30 to 60 grams of Malaga would be an excellent dose. The wine of Bagnols is used in the cordial potion of the French *Codex:* 110 grams of Bagnols, 40 grams of syrup of bitter orange-peel, 10 grams of tincture of cinnamon. Coffee and preparations of caffein may likewise be employed.

Among stimulants, ether may be utilized. Thirty grams of syrup of ether is given in a julep to which four grams of acetate of ammonia are added. Ether may likewise be administered subcutaneously. The injections must be made quite deep into the tissues; otherwise they are very painful, and, what is graver, at times give rise to small eschars. One or two cubic centimetres of pure ether is generally injected, and may be repeated every hour. Du Castel has emphasized the satisfactory effects obtained in variola by the combined treatment of ether and opium. One cubic centimetre of ether is injected morning and evening, and from 6 cg. to 10 cg. of extract of opium are at the same time prescribed, according to the severity of the delirium.

The injections of ether may with advantage be replaced by those of camphorated oil. A 1:3 solution is employed; in some cases one-tenth of ether is added to it. Camphor exercises a powerful dynamogenic action upon the nervous system. It may be administered in the form of enema; in this case it is suspended in a gum arabic emulsion containing in 250 grams of the fluid, 1 gram of camphor, 2 grams of gum arabic, and the yolk of one egg.

Among the nervous disturbances of convalescents we may cite various paralyses which may be treated by two procedures: an internal treatment represented by strychnine, given in doses of 2 mg. or 3 mg. of the sulphate or the arsenate; an external treatment represented by electric currents. If there is albuminuria at the same time, electricity alone is to be employed. Faradic currents are generally used.

Treatment of Cardiovascular Manifestations. Heart disturbances are so frequent and important in various infections that they deserve particular attention and often require special treatment.

The physician has seldom to combat erethism. It sometimes occurs in the beginning of pericarditis. The therapeutic indications consist mainly in revulsive measures: dry or wet cupping over the precordial region and thermocauterization may daily be applied. Coincidently, bromide of sodium or, what seems to be preferable, a mixture of 2 grams of the bromide and 1 gram of iodide of sodium may be prescribed. The vasodilatation produced by the latter medicine diminishes cardiac erethism and the painful phenomena accompanying it. If the latter are very marked, opium preparations, such as Dover's powder or injections of morphine, may at the same time be prescribed. In most cases the period of excitation is transitory and too often yields to a state of depression dependent upon myocarditis.

Whatever may be its cause, myocarditis has important therapeutic indications. The first question arising is: Should the cold baths be continued? It is true that patients who receive baths are less frequently liable to develop myocarditis. When, however, it is developed the baths should be suspended. In fact, the first indication consists in the avoidance of all movement and all displacement of the patient. Coincidently, alcohol or coffee are to be prescribed; injections of ether, of camphorated oil, and, above all, subcutaneous injections of artificial serum, must be practised, the latter, however, in small amounts often repeated. Among cardiac medicines, digitalis is, in this connection, the least effectual; 5 cg. of sulphate of spartein, tincture of strophanthus, or strophanthin, and especially caffein, are to be employed. If the symptoms are not too serious, caffein, given in a potion, will suffice. It is dissolved by benzoate of soda, the influence of which upon oxidations is appreciable. In this case the author prescribes a stimulating potion formulated as follows: rum, 30 grams; syrup of bitter orange-peel, 30 grams; Hoffman's anodyne,[1] 4 grams; tincture of cinnamon, 2 grams; benzoate of soda, 4 grams; caffein, 1 gram; linden flower water, 60 grams. One tablespoonful every half hour is taken.

In case of urgency, subcutaneous injections must be practised. The classical solution is then employed: benzoate of soda, 3 grams;

[1] The French preparation of Hoffman's anodyne consists of equal parts of ether and alcohol, 90°.—Translator.

caffein, 2.5 grams; distilled water, sufficient quantity to make 10 c.cm. Each Pravaz syringeful contains 25 centigrams of caffein; three or four injections may be given in twenty-four hours. When the phenomena of collapse appear, injections of caffein are to be alternated with those of ether, or camphorated oil, or sulphate of strychnine, of which 1 milligram is injected twice a day. Lastly, when arterial pressure is very low—Potain has seen it fall to 13 or even 6 cm.—a little ergotin may be given. In case of fainting, the habitual means are employed: horizontal decubitus, the head a little low, flagellation, artificial respiration, and rhythmic traction of the tongue.

If the patient recovers, he is to be kept on milk diet for a long time, and the avoidance of movements and displacements must be emphasized. Finally, some cardiac medicine must be prescribed, among which I prefer strophanthus (1 to 2 milligrams of the extract or ten to fifteen drops of the tincture). The hypertrophy consecutive to infections requires no special treatment. The treatment of chronic cardiopathies is to be applied—*i. e.*, hygienic precautions and avoidance of fatigue. As to pharmaceutical measures, long-continued medication with iodide and bromide yields the most satisfactory results.

For twenty days each month a daily dose of 1 gram of bromide of sodium and 80 cg. of iodide of sodium, with 20 cg. of iodide of potassium, should be given.

Endocarditis is less frequent and requires no special therapeutics. At the beginning, treatment is the same as in pericarditis. In case of need, cardiac erethism must be quieted by means of revulsives. If the heart muscle shows signs of failure, the same treatment as for myocarditis may then be prescribed.

Vascular and notably arterial complications are very rare. Should the aorta be affected, the treatment must consist in revulsive measures. In the case of peripheral arteritis, the first indication is to place the affected limb in a good position and surround it with hot compresses. When ischemia terminates in sphacelation, subcutaneous injections of antiseptic substances must be resorted to. The author employs neutralized peroxide of hydrogen. Bouchard obtained success by interstitial injections of creosote. Formol and camphorated salol have likewise been employed for the same purpose. If the gangrene extends or the general state is aggravated, amputation must be practised.

Treatment of Respiratory Manifestations. Respiratory disorders require very active therapeutics. In the first place the nasal foci may be the seat of a serous, mucous, or purulent catarrh.

In some cases the inflammation extends to the sinuses of the face. In the case of a simple serous catarrh, a slightly antiseptic powder is snuffed or a little menthol is inhaled. In the case of purulent coryza the best treatment consists in menthol inhalations. The vapor penetrates into the interior of the nose and even the sinuses, and realizes a certain degree of antisepsis. A tablespoonful of a 3 per cent. alcoholic solution of menthol is put in a bowl of hot water, which is then covered with a funnel turned down, and the patient is instructed to breathe the vapors rising through the tube of the funnel. In more serious cases, lavage must be resorted to according to the procedures which we have already indicated. Then a salve with resorcin and menthol must be introduced. The employment of menthol in the form of inhalations and of salves is the best treatment to oppose the development of sinusites. Lastly, it is well to remember that the discharges from the nose often irritate the upper lip; hence the epidermis must be protected by means of a salve, such as vaselin containing boric acid or bismuth. When lesions involve the larynx, menthol inhalations may likewise be employed. The medicinal vapor thus reaches the entire upper part of the respiratory tract. It is advisable, at the same time, to keep the patient in a rather humid atmosphere. For this purpose slightly antiseptic fluids, such as carbolized-water or benzoin-water, may be sprayed about the patient. If the lesions are more profound, notably, if they terminate in the production of ulcerations, stronger medication is necessary. Spraying should be done with Van Swieten's solution,or with naphtholated water. The latter medicine is employed as follows: 25 cg. of naphthol in 25 c.cm. of alcohol and 75 c.cm. of water. In rare cases it may be necessary to touch the larynx directly by certain local medicines. Some medicines administered by the mouth may exercise a favorable action upon the larynx; some of them stimulate the secretions, others diminish the spasmodic element which is superadded to the inflammatory process. Nitrate of pilocarpin is very serviceable in the former case. I inject subcutaneously, at two different times, $\frac{1}{2}$ c.cm. of a 1 per cent. solution. The spasmodic element must be combated by belladonna frequently associated with aconite. A mixture of equal parts of tincture of belladonna and aconite root is used, thirty drops a day in three

doses. Bromides, bromoform, and codein may also be used for the same purpose.

We should like to call special attention to the frequency of extremely troublesome night coughing in certain infections and particularly certain epidemics of influenza. These coughing spells sometimes last an hour or more and give rise to great fatigue. The true treatment consists in giving, at the moment of the spell, one or two tablespoonfuls of the following potion in a little water: bromoform, 1 gram; syrup of codein, 40 grams; cherry-laurel water, 5 grams; white looch, 80 grams.

Applications upon the cervical region are quite frequently practised. They may be employed cold or hot. In the former case the intention is to exercise an antiphlogistic action. Hot applications, however, are being more and more resorted to, as they are antispasmodic, and at the same time stimulate reactions. Laryngeal spasm, notably in young children, may very rapidly be soothed by means of hot applications upon the neck, and at the same time by inhalation of steam. When, in spite of all these medications, the disturbances persist, when the spasm becomes too intense or lasts too long, or when an obstacle to the entrance of air results from deep lesions, pseudomembranes, edema, or ulcerations, the passage of air should be re-established by tracheotomy.

As is known, bronchitis is extremely frequent in the course of the most varied infections. When slight, it needs no particular treatment. When intense, bronchitis does not contraindicate balneotherapy. On the contrary, the baths should be continued, even cold baths; under their influence vascular constriction is produced, which reduces the congestive phenomena. If the individual is too nervous, or if too violent excitation is feared for some reason or other, warm baths at 96.8° or even 100.4° F. (36° or 38° C.) may be given every three hours. This treatment is also indicated when the inflammation extends to the small bronchi and terminates in bronchopneumonia. At the same time applications to the chest may be employed. They are useful in all complications of the respiratory apparatus. The heating compress gives excellent results. A piece of muslin is folded eight or ten times and immersed in water at 59° or even 50° F. (15° or 10° C.). It is then wrung out and applied upon the chest of the patient and covered with oiled silk. At the end of two or three hours the compress is removed. The chest is then found very hot and the skin red and congested, as if a sinapism

had been applied. The treatment acts by the revulsion and the nervous excitation which it induces, which results in deeper respiration and at times in a spell of coughing which expels mucosities.

Cutaneous revulsion may also be practiced by means of large poultices sprinkled with mustard flour, and dry and wet cupping. If the lesions are circumscribed, tincture of iodin may be used to which a little guaiacol is added in the proportion of 2:10 or 5:10, or a salve with guaiacol in the proportion of $1\frac{1}{2}$:10 or 1:10. It is better to abstain from vesicatories which, in an organism already infected, may aggravate the urinary disturbances and even cause cutaneous lesions, and thus open a route for secondary infection. Finally, in children, a more extensive revulsive action may be exercised by prescribing lukewarm mustard baths: 150 or 200 grams of mustard flour is put in a linen bag, which is first plunged into cold water, then into the water of the bath. In very young children revulsion is obtained by means of hot friction. Camphorated chamomile oil is put in a cup and heated over the flame of a candle, and then hot friction is practised with the hand upon the abdomen and lower extremities, which are then covered with a thick layer of cotton. As to the degree of temperature at which the oil is to be used, it is not necessary to determine it accurately. The parents should be instructed to employ it as hot as the hand can bear.

These various procedures are designed to produce revulsion. They sometimes succeed in palliating certain disorders. There is one disturbance, however, which gives much trouble to patients and against which some remedy is always asked: We refer to coughing. Let us remark immediately that coughing, although very troublesome, is nevertheless useful at least in certain instances. We must distinguish two kinds of cough: one is dry and spasmodic, the other favors expectoration. The former may be combated, the latter must be respected, for it is intended to eliminate bronchial secretions or exudates of the bronchi and lungs. Various soothing medicines may be prescribed against dry cough: antispasmodics and especially opium preparations are useful. Nearly all cough syrups contain opium. The following are very often prescribed: Diacode syrup, which contains 1 cg. of extract of opium to 20 grams of syrup; syrup of morphine, containing 1 cg. of this alkaloid to 20 grams of syrup; syrup of codein, 20 grams of which represent 4 cg. of codein; the opiated syrup of lactucarium of the French *Codex*, which contains 5 mg. of extract of opium and 1 cg. of extract of lactucarium in

20 grams of syrup. These various syrups are often mixed with syrup of belladonna and cherry-laurel water.

Even when coughing serves expectoration, it may be combated by the various therapeutic procedures above indicated. For, although it is useful, it sometimes is so troublesome as to disturb the rest of the patient and, therefore, must be moderated. In this case, however, it is advisable to abstain from opium preparations and resort to expectorants. Emetics are at times prescribed for this purpose. This medication, which renders appreciable service, is generally well borne by children. The child being incapable of expectorating, the spasmodic shaking of the cough exercises a sort of massage of the lung, and thus serves for expectoration of the exudates encumbering the respiratory passages. Ipecac, however, which is the only emetic available, should not be administered except when infection is of moderate severity and the child vigorous; otherwise it may cause depression and collapse. On the other hand, an emetic is seldom indicated in adults, and should never be prescribed for those above forty years of age. If bronchial secretions are profuse or the congestive phenomena intense, ipecac is employed in fractional doses. For this purpose Dover's powder may also be employed. The preparations of antimony are likewise regarded as expectorants. Ammonium salts are also useful in this connection. The Germans frequently prescribe hydrochlorate of ammonia. In France the acetate of ammonia is mostly used in doses of from 2 to 4 grams daily. It is usually associated with 20 or 30 grams of syrup of ether. In cases in which the urine is very albuminous, we prefer benzoate of soda in daily doses of from 2 to 6 grams. If after the fall of fever the thoracic manifestations persist, balsamic preparations may be resorted to and, if the process passes to a chronic state, sulphurous medicines may be employed. Among balsamics the balsams of Tolu and terpin are most frequently employed.

These general rules must be supplemented by a few special indications. When there is tendency toward passive congestion the patient must be instructed to lie down in a certain manner. If possible, he should sit in an arm chair or in his bed. He must at least avoid keeping the same position. He should lie down on one side, sometimes on the left, sometimes on the right. The blood circulation is to be modified by means of revulsives and repeated cupping. Certain medicines may likewise serve to regulate the

circulation. Some of them act directly upon the pulmonary blood-vessels, others exert an indirect action through the heart. Among the former, ergotin may especially be mentioned; among the latter digitalis, caffein, and strophanthus. Moreover, if asphyxia occurs, inhalation of oxygen is useful, and in case of need, scarified cupping or a general blood-letting may be practised if the patient is a vigorous subject.

When putrid fermentations are produced in the bronchial exudates, recourse is to be had to substances which, being eliminated by the respiratory passages, may exert an antiseptic action thereon. For this purpose tincture of eucalyptus is generally given in doses of 2 grams, and subcutaneous injections of eucalyptol: 5 to 10 c.cm. of a solution in oil (in the proportion of 2 or 3 per cent.) are injected. Finally, hyposulphite of soda also exercises an appreciable action upon the bronchial secretions: from 4 to 6 grams of it are given daily. All these medications produce no well-marked effect upon the putrefactions of the respiratory apparatus. They seem, however, to act more effectually than inhalations of medicinal substances, such as turpentine and eucalyptus. When a well-localized focus is found in the lung, one is always irresistibly tempted to apply to it some local medicine. Attempts have been numerous, but without encouraging results. Intrapulmonary injections expose to considerable dangers; hence, they have been almost entirely abandoned. The best intervention is evidently incision and drainage of the morbid focus, provided, of course, that the lesion is circumscribed. There is, however, no chance of success except in the case of individuals primarily affected, viz., in those who are sufficiently robust. Even then the operation is always more or less unsafe, especially in view of the danger from secondary hemorrhages, which are of frequent occurrence.

Treatment of Disorders of the Digestive Apparatus. Digestive disturbances often hinder the therapeutics of infectious diseases. Vomiting is observed at the start of a great number of infections. They seem to be dependent upon some disorder of innervation. In the majority of cases the manifestation is transitory and requires no treatment. Should vomiting fatigue the patient too much or last too long, it may be allayed by cold applications upon the epigastric region: an ice-bag is placed or ether is sprayed upon the region. At the same time the patient may be given cold and slightly acidulated beverages to drink; or a small quantity of champagne

with a little Seltzer water may be given. If more active intervention is necessary, the classical potion of Rivière[1] is prescribed. The nature of such vomitings being known, however, we prefer medicines which soothe the reflex sensitiveness of the stomach: chloroform-water and belladonna seem to me indicated. We prescribe a mixture of 100 grams of saturated chloroform-water; 20 grams of syrup of belladonna, and 5 grams of cherry laurel-water, 1 tablespoonful to be taken every hour or half hour. During the stationary period vomiting depends either upon defective secretion or a gastric localization, or else upon some complication.

We often see patients who, under normal conditions, take milk with pleasure and digest it well, while in the course of infections they can no longer bear it; they vomit it in the form of large curds shortly after they have taken it. In this case milk may be mixed with some alkali, such as Vichy, Vals water, and, especially when there is diarrhea, lime-water. Should this prove insufficient, the digestion must be assisted by pancreatin. This may be given in the form of pills after each cup of milk, or 20 to 30 cg. of it may be added to the milk at the time of administration. Another method consists in giving a small amount of beer yeast, which facilitates considerably the digestion of milk.[2]

It should not be overlooked that vomiting is often due to medicines prescribed. Hence, in many cases, discontinuance of a potion suffices to re-establish the digestive functions. In this regard alcohol and cinchona, which are so often abused, have an unfavorable influence which should be remembered. When vomiting results from gastric localization, more active therapeutics must be employed. If the question is one of simple catarrh, lavage of the stomach will render service. If it is due to ulcer, for example, it is expressed by vomiting of sanguinolent matters, and the stomach must be given absolute rest. No nourishment or beverages should be given by the mouth; nutritive enemas and hypodermic injections of salt-water must be given. Ice is to be applied upon the hypogastric region, and opium given either in the form of pills of extract of opium, of which 1 cg. may be administered every hour, or in the form of subcutaneous injections of morphine. The latter method has the advantage of

[1] "Potion de Rivière" has the following composition: potassium bicarbonate, 4 grams; simple syrup, 30 grams; water, 100 grams.—Translator.

[2] Matzoon or zoolak is very often used in America as a substitute for milk when the latter is not well borne.—Translator.

acting more promptly. Moreover, hemorrhages may be arrested by making a sort of gastric dressing by means of subnitrate of bismuth; a large dose of the latter should be prescribed; 15 and even 20 grams would not be too much. Vomiting due to complications requires no special therapeutics. It is dependent upon nephritis, meningitis, perforation of the intestine, and sometimes to inflammation of the diaphragmatic pleura. If, however, it becomes alarming, the vomiting may be combated by the various methods already referred to, and which are to be modified according to circumstances. For instance, opium may be given in case of peritonitis, while this drug is to be avoided when there is uremia.

Finally, at the moment of convalescence, persistent vomiting was formerly observed when the patient was first given nourishment. At present, however, the method of absolute diet having been abandoned, nothing of the kind is any longer encountered. The vomiting of convalescence is due to some complication or to hysteria. In the latter instance, it rapidly yields to the usual procedures. Finally, in consequence of diphtheria, vomiting may depend upon gastric paralysis. It then occurs in the form of regurgitations. In this case lavage may cause death. The introduction of a considerable amount of fluid into the stomach has at times been followed by the rejection of matters which have passed into the respiratory tract. The patients should, therefore, be given small quantities of food, preferably concentrated aliments like thick bouillon. Coincidently, the treatment of paralysis is to be instituted, strychnine given if the urine does not contain albumin, and electricity employed.

In the course of infections the intestine is disturbed more than the stomach. Two morbid manifestations are especially important: constipation and diarrhea. For the treatment of constipation preference should be given to intestinal lavage. If, at the same time, hyperthermia is present, cold enemas may be prescribed, which have the advantage of abstracting heat. In many cases it is well to give an enema morning and evening. The patient may even be instructed to retain the evening enema. This procedure has the advantage of allowing the water to penetrate the organism and, at the same time, softening the fecal matters, which may more readily be evacuated by the enema of the following morning.

We cannot dwell upon the indications of the various kinds of enemas or upon the conditions in which purgatives are to be preferred. There are special rules for each infection. It is well,

however, to remember that a good many physicians dread purgatives in the course of eruptive fevers and erysipelas. In fact, it is better to prescribe enemas or lavage through a tube. If their action is found insufficient, a very mild purgative may be given. In this connection castor oil gives satisfactory results.

Constipation may be accompanied by intestinal paresis expressed by tympanites. In this case very hot or very cold applications should be made to the abdomen. There may at the same time be introduced into the rectum a catheter, which soothes the patient considerably by facilitating the expulsion of gases. Constipation should not always be combated. In certain abdominal lesions, in typhoid appendicitis, and in peritonitis it is a sort of salutary reaction, and is due to intestinal immobility which prevents extension of the lesions. Here an important problem faces us: we must either immediately intervene and extirpate or open the morbid focus by a surgical operation, or else follow an expectant course, and therefore respect the constipation, and at times even increase it by means of opium.

Diarrhea is sometimes to be respected and even favored by means of purgatives. Sometimes it must be checked. The treatment is to be guided by an accurate diagnosis. In typhoid fever the employment of purgatives is of service, especially at the beginning and at the end of the disease. At the beginning calomel may be given; at the end, when diarrhea persists, or when it occurs at the beginning of convalescence, attended by some febrile movement, a saline purgative produces excellent effects. The action of purgatives during the stationary period is more contestable. They are said to increase meteorism and favor perforations. I believe this opinion not to be well founded, and think that in most cases a saline purgative may be prescribed every five or six days. Moreover, this is an excellent means of accomplishing intestinal antisepsis. For the same reason a purgative also succeeds in the majority of infectious diarrheas. When, however, the general state of the patient is grave and the alvine evacuations are abundant, giving rise to cold, spasms, and cyanosis, I believe it is better to employ antidiarrheal substances, such as subnitrate of bismuth. This is given by the mouth in doses of from 4 to 6 grams, and, if necessary, from 10 to 20 grams may be introduced into the intestine through a tube. This furnishes a dressing comparable to that practised for the stomach. Bismuth is generally associated with some insoluble antiseptic, and the treat-

ment is completed by the administration of milk mixed with lime-water, rice, and some stimulants, such as tea with rum, and ether, to which injections of camphorated oil may be added in grave cases.

Whether purgatives or constipating medicines are resorted to, it is always advisable at the same time to utilize enemas and still better profuse intestinal irrigations with boiled salt-water or antiseptic substances. The putrefied substances and microbes are thus mechanically thrown out.

Gastrointestinal disturbances readily involve the liver. In most cases it will suffice to continue the general treatment. Profuse intestinal irrigations with cold water at 53.5° or 59° F. (12° or 15° C.), as well as an absolute milk diet and cold baths, are particularly to be insisted upon. As a more special medicine we may cite calomel; a small dose of 1 or 2 cg. given every morning produces satisfactory results. The special action of ether upon the liver has already been explained. Let us add the rôle of salicylic acid and its derivatives, notably salol. This medicine has the triple advantage of being cholagogue, of decreasing the pain produced by inflammation of the biliary passages and of realizing a relative antisepsis in these passages. In cases of renal lesions the salicylates are not well borne. Hence, benzoate of soda should be substituted therefor.

Treatment of Renal Disorders. Alterations of the kidney in the course of infections often embarrass therapeutics by contraindicating the employment of certain active medicines. These lesions may be treated by revulsion at the beginning, or by dry or scarified cupping applied to the lumbar region. If hematuria appears, ergotin or, still better, calcium chloride, is given. Then the oxidizing method is resorted to; from 2 to 6 grams of benzoate of soda are prescribed. It is understood that the patient is to be put on an absolute milk diet. In many cases satisfactory results will be obtained by diminishing the formation of autogenic poisons by means of antisepsis and profuse irrigation of the intestine.

Albuminuria, which sets in during convalescence, is to be treated as during the stationary period. When it becomes chronic the milk diet cannot be prolonged indefinitely. While some patients bear it well, others experience marked disgust and vomit the milk every time they take it.

The diet must then be modified. Coffee or rice may be added to milk, some vegetables, eggs, and, if desirable, white meat may be permitted. Instead of bread, dry toast should be given. In general,

diuretics are useless. If any are to be used, theobromin should be prescribed. It is better to favor diuresis indirectly by cold enemas, oxidants, and especially benzoate of soda. In certain cases tannin, if it is well borne by the stomach, proves serviceable. Stronger medicines seem to be contraindicated. In a case of albuminuria with a slow course, consecutive to scarlet fever, the author prescribed one drop of tincture of cantharides. This little dose sufficed, however, to produce hematuria and aggravate the previous symptoms.

CHAPTER XXIV.

HYGIENE AND PROPHYLAXIS OF INFECTIOUS DISEASES.

Individual Hygiene. Isolation of the Patient. Precautions to be Taken by Those Waiting upon the Patient. Hygiene of the Sick-room. Disinfection of the Bedding and Linen. Sterilization and Destruction of Secretions, Excretions, and Squamata Cleanliness. Alimentation. Beverages. Hygiene of Convalescents. Social Hygiene. Quarantine. Isolation Hospitals. Transfer of Contagious Cases. Declaration of Contagious Diseases. Municipal Service of Disinfection. Vaccination. Variolization. Syphilization. Vaccine. Personal Statistics Showing the Influence of Vaccine upon the Course of Variola. Vaccination by Means of Attenuated Viruses. Anthrax Vaccine. Vaccination against Hydrophobia. Vaccination by Means of Sterilized Cultures. Attempts at Immunization against Cholera and Typhoid Fever. Prophylactic Injections of Serum. Application of the Serum Method to the Prophylaxis of Diphtheria, Puerperal Fever, Tetanus, and Bubonic Plague. Conclusions.

Individual Hygiene.

Hygiene of the Sick Room. The therapeutics of infectious diseases, notwithstanding its considerable interest, is perhaps less important than the hygienic measures which must be observed with reference to the patient and those surrounding him.

In the case of a contagious disease, perfect isolation of the patient is the first requirement to be met. To this end it is necessary to have two rooms at one's disposal, one in which the patient will lie; another, contiguous thereto, which will serve for disinfection of persons who have approached the patient and the objects which have come in contact with him. In certain instances it is preferable to have a suite of three rooms, two of which will serve the patient, one during the day, the other during the night. The number of persons charged with the care of the patient should be at least two, and it is indispensable that these persons should have no other occupation and fulfil with accuracy the prophylactic measures indicated to them.

Before entering the room of the patient the visitor should put on a blouse, and it is well to protect the hair by means of a cap, and to change the shoes. If the last-named precaution is not taken, it will be necessary to spread in the disinfection room a crash of several thicknesses, which has been sprinkled with a 2:1000 solution of corrosive sublimate, on which the shoes should be rubbed on passing

out of the patient's room. Then the face and hands should be washed with a 1:2000 solution of corrosive sublimate or 1:1000 solution of oxycyanide of mercury; if the person wears a beard it is indispensable to cleanse it well with the same fluids. Persons waiting upon the patient should never eat or drink in his room. The meals should be taken in another room after having changed the clothing and disinfected the hands and face. They should not carry their hands to their face without being disinfected, and the handkerchiefs which they may have to use in the patient's room should not be used outside. It is also indispensable for a parent to abandon the unwise habit of kissing the patient: they should avoid every unnecessary contact with the patient.

The sick room should be large and well ventilated, with southern or eastern exposure. The windows should be furnished with Venetian blinds, which are to be kept closed in certain infectious diseases, such as measles, variola, and sometimes erysipelas. The red glasses advocated by Finsen for the treatment of variola, and at times employed in measles, do not seem to be useful. Red light often exerts a too intense excitation upon the nervous system, while green light seems to be better borne. The hangings of the room should be removed, as well as all useless objects and curtains. The bed of the patient should be placed in the middle of the room, or at least far from the walls, so as to be approached from any side. There should be, especially in cases of obese patients, some contrivance designed to enable the nurses to raise the patient easily for cleansing without tiring him. If the skin shows a tendency to develop bed-sores, the bedclothes should be sprinkled with talcum or cinchona powder, and pneumatic rings or water cushions should be used.

When possible two beds should be placed, with a bath-tub between the two. When the patient has taken a bath he should be put in the second bed and, while he is resting there, the other bed should be aired and properly arranged. In this manner after each bath the patient may lie down in a comfortable bed. The physician should pay particular attention to the ventilation of the room. In summer the windows may be left open for the greater part of the day. During the night the window of the adjoining room is to be left open, and a screen should be placed so as to protect the patient from the draught of cold air. In winter the ventilation of the room should be assured by means of an open fireplace, where a fire should be kept up night and day. For ventilating the room the window of the

adjoining room should be opened. If it is very cold, the latter room must also be heated; while the window is open the door between the two rooms should be kept closed. The temperature of the sick-room should not be very high; it should be kept between 61° and 64° F. (16° and 18° C.).

Cleansing and Disinfection of the Room and Objects; Sterilization of Morbid Products. The cleansing of the room should not be made by sweeping, which raises dust, but by means of a mop wet with a solution of corrosive sublimate.

According to the disease treated, the patient may be permitted to rise to attend to his natural wants, or the bed-pan may be employed. This measure is indispensable in typhoid fever. The dejecta must always be disinfected before they are disposed of. A 2:1000 solution of corrosive sublimate, or a 50:1000 solution of copper sulphate, or lime-water, should be poured into the bed-pan. The urine should be collected in the adjoining room, and after the amount voided in twenty-four hours is measured, it should be disposed of. In certain cases, however, it is advisable to disinfect the urine. The urine in hemorrhagic variola and that of typhoid patients, when they contain albumin and the germs of the disease, are so to be treated. The various discharges and secretions are to be taken upon absorbent cotton and thrown into the fire. The sputa must be disinfected by means of antiseptics or boiling. If there is desquamation, the squamata that fall in the bed-clothes should be burned. If any should fall on the floor, they should be picked up by means of a wet cloth. The patient should have exclusively his own eating utensils. These should be cleansed in the adjoining room, first plunging them into boiling water. The instruments serving for the usual explorations, such as the tongue depressor or the spoon substituted for it in examining the throat, should also be sterilized. In our wards we employ glass tongue depressors, which are very easily sterilized. Of course, the various canulas, catheters, as well as thermometers, should also be disinfected. It is advisable to immerse all the linen of the patient in an antiseptic fluid, thus preventing the possible dissemination of dried products and squamata until they are sent away for disinfection. A solution of lysol serves this purpose well.

During the course of the disease, and especially during convalescence, the patient often asks to write. If his desire is to be complied with, the paper should be sterilized by means of sulphur or formol vapor. When he begins to get up he must put on clothing which

may be disinfected afterward. Finally, after a certain period of time he may be permitted to resume his ordinary occupation. It is difficult to determine at what moment a convalescent individual is no longer contagious. The period of isolation has been fixed at sixteen days in measles, varicella, and mumps, and at forty days in scarlet fever and variola. These averages are acceptable. The author believes, however, that the quarantine in cases of measles may, without any inconvenience, be reduced. For varicella and variola, isolation may be abridged in mild cases, when there are only a few eruptive elements and the desquamation is complete. On the other hand, after a confluent variola, if the crusts persist at the end of forty days, the danger of contagion has not yet disappeared, and isolation must, therefore, be prolonged.

In case of diphtheria, cultivation is often resorted to; as long as Loeffler's bacillus is found isolation is to be maintained. If at the end of three weeks the microbe has disappeared, an inoculation into the guinea-pig is advisable. These precepts are perhaps good, but they have the great inconvenience of not being sufficiently practical. One may, therefore, be contented with isolating the patient for three weeks, then he should be advised to practise for at least a month, morning and evening, cleansing of the mouth by means of boiled water to which thymol is added in the proportion of 1:1000.

When it is thought that the patient needs no longer to be isolated, he must be given in the adjoining room a last antiseptic bath with corrosive sublimate or naphtol. If possible, his hair should be cut very close; at all events, complete cleansing of the scalp with soap and then with some antiseptic water should be made, this to be followed by rubbing with alcohol. After the bath, the patient should put on clean clothing, and leave definitely the rooms in which he has been treated. These rooms are then to be disinfected by means of hot corrosive sublimate solutions or vapors of sulphur or formaldehyde. In our wards, after cleansing with corrosive sublimate, we burn 30 grams of sulphur per cubic metre of space. The locality is kept closed for twenty-four hours. Moreover, all objects of little value which have been used by the patient, such as toys and books, should be burned. It is understood that domestic animals must not be allowed to enter the patient's room, for their hair becomes charged with infective products, which may then be easily disseminated.

Hygiene of the Sick. During the course of infection cleanliness of the patient must be constantly attended to. If there is no special

reason for the employment of balneotherapy, it is advisable, as a hygienic measure, to give the patient a lukewarm bath of fifteen or twenty minutes every day or every other day. After each meal the mouth of the patient must be cleansed. After each injection the urinary organs and anus should be cleansed. Likewise, the mouth is to be cleansed every morning with Vichy water or borated solution, the teeth brushed, and a small amount of mentholated pomatum introduced into the nostrils; the cutaneous abrasions must be dressed and, in case of desquamation, a little vaselin should be spread upon the skin. It is also very useful to prescribe daily one or two enemas in order to cleanse the lower portion of the intestine. A little precaution which should not be overlooked at the beginning of infectious diseases is to remove the jewels, rings, and ear-rings of the patient. In case of erysipelas, ear-rings may give rise to a sphacelus in the inflamed lobe. In several cases the author has seen the fingers swollen under the influence of the variola eruption and so strangulated by rings that the cutting of those ornaments became a difficult matter.

Alimentation. As has already been stated, patients must be fed during infections. As a general rule, they should be given milk, bouillon, and a certain amount of beverage, but care should be taken to give a very small amount of liquid each time. The best practise is to give a glass or a glass and a half of milk every hour. Vichy, lime-water, or pancreatin may be added to the milk. If this nourishment is not kindly borne, a little beer-yeast may be given, or the milk may be replaced by some other substitute. (See footnote, page 832.) The amount of milk varies according to the case: it may be said to be for an adult two quarts (two litres) a day. In cases of scarlatina milk must be the only aliment; no bouillon is to be permitted, but some beverages sweetened with syrup of currant or pomegranate, or sweet barley-water. The milk diet being absolute, three quarts of it must be given daily for twenty days. At the end of this time if the urine contains no albumin a more substantial alimentation may be resumed, such as bouillon, rice, creams of vegetables, eggs, and, four or five days after, even meat may be given. Should some albumin appear in the urine, the absolute milk diet should again be instituted, which is to be discontinued eight or ten days after the disappearance of albuminuria.

In most other diseases, including typhoid fever, two quarts (two litres) of milk and one quart (one litre) of bouillon are generally

given. Dr. Robin also prescribed beef-tea prepared by heating small pieces of meat with one quart (one litre) of bouillon in a double boiler. In order not to coagulate the albumins, care is to be taken not to raise the temperature above 140° F. (60° C.). Bouillon has the advantage of acting as a peptogen and, at the same time, introducing into the organism salts to compensate for the loss of mineral matters. The amount of salts is from eight to ten grams in a litre (1000 c.cm.). Vegetable infusions may likewise be utilized. A very good preparation consists in mixing one part of barley-water with two of milk; this is preferably sweetened with honey. This mixture is often very well borne by those who do not like milk. When, however, the repugnance for milk, experienced by some patients, cannot be overcome, one is compelled to resort to some other alimentation. Bouillon and also bouillon with an egg added to it (*lait de poule*). It is well to complete the diet by a small amount of alcoholic beverages: according to the case, vinous lemonades, Malaga or Bagnols wine, and Todd's potion. Coffee may also be permitted in the proportion of 10 grams for 200 grams of water.

The diet above indicated has not seemed sufficient to certain physicians who at present nourish their patients substantially. As a matter of fact, three or four quarts (three to four litres) of milk must be given in order to meet the wants of the economy. So great a quantity is too much for some patients to bear. Moreover, milk contains an inadequate proportion of albumin and carbohydrates, and an excess of fat. It is necessary to increase the administration of nitrogenous aliments. This is what was done by the addition of bouillon. At present several Russian physicians go farther. Dr. Vaquez, who has tried the new method in typhoid fever, advises a cup of milk every other hour only; at 8 A.M. he gives, instead of milk, café au lait or a soup with milk, and some flour or rice. At noon and at 6 P.M. milk is replaced by a meal composed of some soup or a bouillon containing the yolk of an egg and a small cup of meat jelly, or fresh meat juice. At the end of the disease, raw meat, preferably chopped mutton, is given. Two or three days after the fall of the fever, creams of vegetables are given, and toward the eighth day eggs, dry toast, and stewed fruits are allowed.

By thus nourishing the patient, we succeed in preventing adynamic manifestations and abridging considerably the period of convalescence. Intestinal disturbances, perforations, hemorrhages, and consequent relapses were feared; according to published observations,

however, this apprehension is not well founded. The feeding having been continued during the entire course of the disease, its increase at the time of convalescence gives rise to no disorder. On the contrary, it is known how frequent are relapses in those cases which are subjected to milk diet, when the patients are too soon permitted to take substantial food.

Barring the case of typhoid fever, the author thinks that in all other infections except scarlatina a sufficiently plentiful and varied alimentation may be allowed without any fear. The author gives milk, bouillon, eggs with soups and particularly barley and rice soup, according as there is tendency to constipation or to diarrhea. This diet seems to him especially important in variola. His experiments demonstrated that abundant alimentation often enables animals to resist the inoculation of variola. In some cases, however, we may have some difficulty in overcoming the resistance of patients whose throats are covered with pustules and who suffer when they swallow food. In such cases, gargling with an infusion of cocoa leaves should be prescribed or the throat painted with a cocaine solution before each meal. Should these methods fail, the patient should be fed by means of a tube introduced through the nose. Should albumin appear in the urine the patient should be put on milk diet, eggs, and rice. The same alimentation, with the same restrictions, is to be employed in diphtheria. During convalescence the patient should be given more liberal nourishment. If there are renal complications and albumin in the urine, the diet should be limited to milk, coffee, raw eggs, and rice, a small amount of farinaceous food in the form of puree and stewed fruits. No meat is given, and instead of bread, dry toast. If paralysis of the palate develops, notably as a result of diphtheria, purees are the aliments most readily accepted by the patient. He must be advised to swallow the liquids with the head thrown back, and to drink very slowly, lying on his back so as to cause the fluids to flow according to the laws of gravitation.

In conjunction with the aliments a certain amount of beverages is to be allowed. The thirst experienced by the patient clearly indicates that his organism wants water. Slight infusions, sweetened, should be given. Milk not being sufficiently rich in carbohydrates, it is well to put sugar in the beverages. For the same purpose boiled lemonades, vinous lemonade, and some Vichy may be given with a little syrup. If the stomach does not tolerate fluids well, the beverages should be replaced by enemas, which the patient must retain. In

such cases subcutaneous injections of artificial serum yield gratifying results.

Hygiene of Convalescents. During convalescence, diet is to receive special attention. Nourishment must be progressively increased and the patient gradually allowed to return to his habits in the matter of eating, but the digestive functions must be carefully watched. If flatulence, slow digestion, hypochlorhydria or hyperchlorhydria occur, the various classical treatments of dyspepsia should be employed. The intestinal function also requires attention. Exaggeration of gastrointestinal putrefactions, constipation, and diarrhea and mucomembranous enteritis are not rare in consequence of infections. At all events, the convalescent must be instructed to eat slowly and masticate well, and take at least four meals daily. After each meal he must take a rest for an hour, either sitting or lounging, and a little more covered than usual, since a convalescent is more sensitive to cold than normal subjects. It is, therefore, advisable to give them warmer clothing and to have their room at a higher temperature than usual. The room must be well ventilated: in summer the windows should always be kept open, and during the night those of the adjoining room. Exercise must be moderate and progressive. It will be useful for a certain length of time to continue to take the rectal temperature, at least in the evening. An elevation in the temperature often announces that alimentation is not well borne or that exercise has caused too much fatigue. When convalescence is well established it is desired, whenever possible, to send the patient to a summer or winter resort, according to the season.

The author cannot too much emphasize the necessity of devoting continued attention to the toilet. A convalescent should take slightly tonic sulphur or salted baths. He must rub his body every morning for five minutes with a Turkish towel or rough flannel wet with some alcoholic preparation, for example, lavender brandy. In order to be able to judge the efficacy of these measures, it is advisable to weigh the convalescent once a week and examine his strength by means of the dynamometer. If the functions are not re-established with gratifying rapidity, bitters should be prescribed in case of anorexia, and tonics, such as lecithin, in case of weakness. In such cases subcutaneous injections of artificial serum are also practised. Finally, the alimentary method may be modified, and raw meat, for instance, may be recommended.

Social Hygiene.

The advice above presented with reference to the hygienic treatment and isolation of patients is not always easy of application. In order to isolate a contagious case, two persons should be assigned to his service exclusively. Among the poorer classes, when several individuals occupy one room, isolation is impossible. What further aggravates the situation is that patients are attended by parents, friends, and sometimes the janitor, and that persons thus approaching the patient return to their occupations without taking any antiseptic precautions. Hence, epidemics ravage the crowded sections of cities and make certain tenement-houses centres of infection.

While certain laws have been promulgated for preventing the importation of epidemics from foreign countries, hardly any measures have been taken to insure isolation of contagious patients in domestic epidemics. The only progress up to the present time realized in France has been the establishment of services of disinfection, of vaccination at home, and of transportation of contagious patients in special vehicles and urban ambulances. It is, of course, out of the question to isolate all contagious cases. Only those individuals who suffer from acute infections may be isolated in appropriate institutions. When the question is one of chronic infection, such as tuberculosis, other measures are applicable. A fight against the latter disease has been undertaken with gratifying results. The public is warned by means of placards in public establishments, surface cars, wagons, not to spit upon the floors, and in a good many establishments hygienic cuspidors have been placed; public lectures and popular books on tuberculosis have been published. Moreover, sanitariums and rural colonies have been created. There are already more than a hundred of these in France alone.

Declaration of Contagious Diseases; Disinfection by Officers of the Board of Health; Transportation of Patients. The law of November 30, 1892, obliges every physician, under penalty of the law, to pay a fine of from fifty to two hundred francs to declare to the public authorities the cases of contagious diseases coming under his observation in the course of his practice. The present list includes the following twelve diseases: typhoid fever, typhus fever, variola and varioloid, scarlatina, diphtheria, sudor anglicus, cholera and choleriform maladies, bubonic plague, yellow fever, dysentery, puerperal infections, and ophthalmia of the newborn. Certain milder infec-

tions, such as mumps, varicella, and whooping-cough, have been left out, as also others that are not very contagious, such as erysipelas, or are contagious for a short time only, such as measles. It would, however, be advisable to add pneumonia to the list.

When patients ask to be treated outside of their homes they are transported in particular vehicles and their residence is disinfected free of charge—these are gratifying advances. It seems to the author, however, that it is high time to take serious prophylactic measures, and thus complete the law of 1892. It is necessary to determine in what diseases isolation shall be compulsory. When the residence of the patient does not permit isolation under sanitary precautions, such cases should be transported to a special hospital. It is also necessary to determine the average duration of contagiousness and engage the civic responsibility of every individual who places himself in a position to directly or indirectly contaminate his fellow citizens.

Finally, there remains a last question. There is a fearful disease against which we possess an infallible prophylactic means, namely, variola. The measures indicated above should be completed by a law bearing on compulsory vaccination. We are thus led to the study of a question which, from a sociological standpoint, is of prime importance, that is the question of vaccination.

Vaccinations. The term vaccinia, which signifies disease of the cow, primarily designated an eruptive infection afflicting cows and horses, which is transmissible to various animal species and notably to man, confers upon the latter immunity from vaccinia and variola. Vaccination is the inoculation into man, with a prophylactic view, of the disease of the cow. The sense of the term has gradually been broadened considerably, and to-day under the name vaccination are included the various methods which are capable of conferring immunity against a future infection or preventing the development of a disease while at its stage of incubation.

At present we are acquainted with a number of methods which enable us to confer immunity and thus practise preventive medication. For the convenience of description the principal procedures advocated may be grouped under six classes:

1. We may inoculate the disease against which we wish to preserve the individual. This method, the most ancient of all, has been utilized against variola. It was proposed by Auzias-Turenne against syphilis. It is still employed in veterinary medicine for protecting

animals from symptomatic anthrax, murr (foot-and-mouth disease), and peripneumonia.

2. A benign disease may be inoculated to preserve the individual from a grave disease. Such is the case with vaccinia, which seems to be a disease different from variola and preserves the individual from the latter.

In the two preceding cases a non-modified virus is introduced into the organism.

3. The third method consists in inoculating a virus which has been partially freed from its noxious properties. This method is often designated Pasteurian vaccination. It is employed as a prophylactic in animals, notably against anthrax, and with a therapeutic view in man, especially against hydrophobia.

4. Instead of inoculating attenuated although still living microbes, the products secreted by bacteria may be employed, as is often done in laboratories. Such is the method initiated by Ferran against cholera, and which is utilized by Haffkin against bubonic plague.

5. Having remarked the analogy existing between the action of certain toxins and that of certain substances of vegetable origin, Peyraud endeavored to learn whether some poisons of a more or less definite chemical character could not preserve from infections. These chemical vaccinations might be utilized against tetanus and hydrophobia. Strychnine is expected to confer immunity from the former of these two infections, and the essence of tansy from the latter.

6. Finally, therapeutic serums are not merely curative; they may be utilized as preventives. Antidiphtheritic, antitetanic, antistreptococcic, and antibubonic serums have been employed for this purpose.

Immunization by Means of Strong Viruses. VARIOLIZATION AND SYPHILIZATION. Variolization is a very ancient method which has come to us from China. It was first introduced into Persia, thence into Turkey, in 1673, by E. Timoni and J. Pylarini. In 1721 the wife of the British ambassador in Constantinople, Lady Montague, who saw the fairly satisfactory results obtained by this procedure, brought it to the knowledge of her friends on her return to London. The new method spread quite rapidly, and was very happily modified by two Scotch farmers, Suttey brothers, who invented subcutaneous inoculations. Inoculation of the variolar virus commonly induces a benign disease. It is not difficult to comprehend the difference

which separates the evolution of the inoculated disease from that of the spontaneous malady. In the case of inoculation the pathogenic agent is introduced beneath the skin—*i. e.*, into a region that is not favorable to its development. As a matter of fact, the spontaneous disease probably results from inoculation into the respiratory apparatus. The result is analogous to that observed when the virus of tuberculosis or even of glanders is introduced beneath the skin; the infection is exhausted in local symptoms, and with difficulty invades the entire economy. On the other hand, immunizing inoculation is practised upon normal individuals who are in good health and in nowise predisposed to infection. On the contrary, the spontaneous disease attacks debilitated individuals, or at least those whose resistance is weakened by a series of predisposing or auxiliary causes. Variolization, however, is not always harmless; the inoculated organism may be found in such conditions of predisposition as to favor generalization of the infection, which may then assume a serious course, and at times terminate fatally. Moreover, even if the inoculated individual resists, the few pustules which develop may become the means of propagation of the infection, and thus constitute a danger for others. A starting point of an epidemic may thus be created.

Although variolization has rendered some service, it must be abandoned at present and give way to vaccination. Can the method be applied to other diseases? We have above alluded to syphilization. As is known, Auzias-Turenne endeavored, in 1844, to accomplish with regard to syphilis what was done for smallpox. At that time, however, soft chancre was not differentiated from the indurated variety. The virus of the soft chancre was inoculated. Auzias-Turenne injected pus and repeated the inoculations. There came a moment when at least a relative immunity was acquired: the soft chancre no longer developed or appeared under a mild form, and the author believed he had thus conferred immunity against syphilis. When, in the Congress of 1867, it was pointed out to him that he had inoculated a virus different from that of syphilis, Auzias-Turenne modified his theory. On the ground of the immunity conferred by vaccine against variola, he argued that the virus of soft chancre may immunize an individual or cure him. Experiments failed to verify this conception. Individuals who were inoculated a great number of times—287 times in a case of Danielssen—contracted the indurated chancre when the syphilitic virus was em-

ployed. Sperino's idea of combating syphilis by means of repeated inoculations with the virus of both soft and indurated chancres has not yielded any better results. The method was therefore abandoned. Its failure should not, however, lead us to overlook the fact that Auzias-Turenne pursued interesting experiments on animals and that he had the honesty to begin upon himself the researches which he wished to pursue on man; finally, although he failed from a practical standpoint, he set forth some interesting considerations, and seemed to have a foresight of exaltation and attenuation of viruses.

At present no strong viruses are inoculated into man, but they are inoculated into animals. This is the principle of the method employed against symptomatic anthrax, murr (foot-and-mouth disease), and peripneumonia. In order to render the inoculation inoffensive, it is practised in those regions of the body in which a thick cellular tissue offers a certain resistance to the multiplication of the pathogenic agents.

Antivariolar Vaccination. The inconveniences of the preceding methods are no longer found in the case of vaccinia.

It had long been known in certain regions of England, and notably in the county of Gloucester, that individuals breeding cows often presented in their fingers small pustules contracted on contact with animals afflicted by cowpox, and that this eruption conferred upon them immunity from variola. In 1768 Sutton and Fewster drew attention to these facts. It was then that Jenner conceived the idea of practising in a systematic manner and with a prophylactic view the inoculation of cowpox. In 1798 he published the result of his researches. He demonstrated the inoculability of cowpox from cow to man, and its transmission from man to man, and showed that immunization was surely conferred by the inoculation of the vaccine.

The interesting question was then and still is asked: What are the analogies existing between vaccinia and variola? It is certain that clinically the two diseases are absolutely distinct. To be convinced of this it suffices to examine a man attacked simultaneously by both of these diseases. The objective characters of the variola and of the vaccinal pustules are not at all similar. At present, however, when we are well acquainted with the variability of viruses, we may ask whether the differences are as great as one might believe, whether vaccinia and variola do not have a single origin, and whether the virus has not been modified through repeated passages in man

and in animals. Dualists, among them Chauveau, remark that the objective characters are different, that the receptivity of animals is not similar, and particularly that the variolar virus is not transformed into vaccinia through passages in cows. The latter argument is not perhaps irrefutable, for it may be answered that inoculations in series have not been sufficiently numerous. On the other hand, the fact itself has been contradicted. Voigt (1881), Fischer (1885), Eternod and Haccius (1892) assert that by practising inoculations on large surfaces they have transformed variola into vaccinia, and, transferring their experimental results to the domain of practice, they have prepared a vaccine of variolar origin which has given excellent results.

Although the question presents great theoretical interest, it seems to be of little consequence from a practical standpoint. Vaccinia, which seems to be weakened when it is inoculated from man into man, according to the Jennerian method, preserves all its activity when it is cultivated in cows. A second problem, however, arises. Its human origin being denied, it remains to learn whether vaccinia is originated in the cow or in the horse. Jenner supposed cowpox originated from horsepox, and described the disease of the horse under the name "grease." This gave rise to confusion. The word "grease" was translated by the expression "eaux aux jambes"—an expression applied to osteitis of the foot. It was not until after the contributions of Sarrans and Lafosse that it was understood that Jenner's grease is the disease of the horse, formerly designated under the name "morve volante" (flying glanders). Lafosse showed that the virus is readily inoculated from the horse to the cow, and that it produces in the latter a typical vaccinia. Chauveau showed later on that the inoculation of horsepox produces in children an aborted vaccinia only; he concluded therefrom that vaccinia acquired all its activity in the cow, and that it represents a bovine infection and not an infection of the horse. It is to be noted, on the other hand, that vaccinia is transmissible to a great number of animal species, notably to dogs, sheep, goats, and, at least in certain cases, to rabbits.

At present it may be stated that the vaccinal virus, owing to numerous passages which it has undergone in cows, has become a fixed virus: its inoculation is almost invariable. In individuals vaccinated for the first time, the eruption begins seventy-two hours after inoculation, and is clearly manifest in the course of the fourth day. Even with this fixed virus, however, certain variations are

observed. The incubation often lasts four or five days, exceptionally six or seven.

The inoculation is generally practised by three epidermal punctures or, still better, by superficial scarifications. The eruption is localized at the infected points, and it is altogether exceptional to see it generalize. In the latter case the disease assumes the character of a quite serious infection, accompanied by fever. Even some cases of death in young children have been reported. This eventuality, however, is so extraordinary that it hardly deserves to be taken into account. The generalization evidently indicates a peculiar susceptibility to vaccinia, and probably to variola. Barring these facts, examination of the local lesion produced by inoculation likewise demonstrates that individuals, according to previous diseases or vaccinations, according to their innate or inherited characters, even according to a number of intercurrent circumstances, present peculiar resistance or susceptibilities. The regular vaccinia begins on the third day with a papule, which is transformed into a vesicle on the fifth, and reaches maturity on the seventh. At this moment the lesion is constituted by a large flat, umbilicated vesicle, surrounded by a red areola and containing a clear and thick fluid. Toward the eleventh day the crust appears, which is exfoliated from the twenty-first to the twenty-eighth day, leaving an indelible cicatrix. In certain instances the evolution is more rapid, the vesicle remains small, and, within a few days, its evolution is terminated. This vaccinoid, which has improperly been called pseudo-vaccinia, simply indicates a slight resistance of the organism, and it seems to me to prove that immunity requires to be reinforced in such cases.

The evolution of vaccinia is followed by a modification in the body fluids, which has been clearly demonstrated by the researches of Sternberg, Beclère, Chambon, and Ménard. This is a particular instance in perfect harmony with our present knowledge of the mechanism of artificial immunity. As always, however, the modifications thus produced in the organism are not permanent. At the end of a certain length of time immunity disappears. It is generally estimated that adults should be vaccinated once every ten years; children whose nutrition is more active more rapidly lose their vaccinal immunity, and must be revaccinated once every seven or eight years. These data are perfectly acceptable. It should be remembered, however that one vaccination does not suffice to extinguish variola in a definitive manner. The countries where

vaccination is compulsory are not free from the disease. For example, in Sweden, where the mortality was 165 per 100,000 inhabitants before the introduction of vaccine, fell, since the discovery of vaccination, to 55, and since vaccination was made compulsory, to 18. In Germany, where law prescribes vaccination and revaccination, the mortality is only 2.2 per 100,000 among the civilian population, while in the army, in which the rules are better observed, variola may be said to be unknown. It would, therefore, be easy, through an international agreement, to cause the disappearance of variola. So far as France is concerned, we know at present that variola, although sufficiently rare, is still observed, particularly in certain cities, such as Marseilles. In 1900 we had in Paris a quite severe epidemic, which continued and even increased the following year. At the time an epidemic is prevailing the resistance conferred by previous vaccinations should not be counted upon; variola itself does not create absolute immunity. A certain number of recurrences have been reported, and Heim, by revaccinating individuals who had once had variola, obtained 32 per cent. of complete successes, 25 per cent. of incomplete successes, and 42 per cent. failures. According to the wise advice of Dr. Hervieux, in ordinary times individuals should be vaccinated at the age of ten, and then again at the age of twenty. At the time of an epidemic, however, everybody should be vaccinated. It is also to be remembered that the aged are not refractory, as is generally supposed. Facts recorded by Beclère and Brot[1] are absolutely conclusive. Everybody should, therefore, be revaccinated, since the duration of immunity is not fixed, and it is not known at the end of how much time it disappears. Thus, in 1897, we noticed that vaccinia succeeded for the second time in six children, the oldest of whom was five years and the youngest sixteen months old.[2] In all of these indubitable cicatrices of a previous vaccination were present. These subjects were, therefore, in a state of receptivity. Several personal observations of mine could be cited in support of this conclusion. The most interesting of these observations is that concerning a pregnant woman, already referred to (p. 590), who had been successfully vaccinated at the seventh month of her pregnancy, and two months later contracted a benign variola which she communicated to her child, The latter, owing to the influence of the maternal vaccination, resisted the infection fairly well.

[1] Brot. De l'immunité vaccinale. Thèse de Paris, 1897.

[2] Roger. Sur la durée de l'immunité vaccinale. Société de Biologie, July 2, 1897.

The conclusion is unavoidable: at times of epidemics everybody must be vaccinated. At ordinary times revaccination should be practised once every ten years. It is also to be remembered that if a previous vaccination does not secure absolute immunity from variola, it decreases the gravity of the infection and that the mortality is very low in revaccinated individuals. Of individuals who have been vaccinated three times we have lost only three in our wards.

The statistics of the Westham-Union Hospital, bearing upon 1000 cases observed from 1877 to 1882, furnished the following results, which need no comment:[1]

	Cases.	*Mortality.*	*Per cent.*
Non-vaccinated variola	117	59	50.4
Not well vaccinated	78	19	27.1
Vaccinated variola cases	792	85	10.7
Vaccinated and revaccinated cases	21	0	0

Dr. Delom[2] who, from this point of view, tabulated 1023 observations taken in our hospital in 1900 and at the beginning of 1901, obtained the following results:

	Cases.	*Mortality.*	*Per cent.*
Non-vaccinated	77	52	67.5
Vaccinated once without success	18	8	44.4
Vaccinated once with success	700	159	22.7
Vaccinated with success and revaccinated without success	100	13	13.0
Vaccinated and revaccinated with success	89	14	15.7
Vaccinated while in incubation of variola	39	8	28.5

If the age of the individual is considered, the following interesting results are obtained, which we sum up as follows:

Age of patient.	Non-vaccinated.			Vaccinated once.						Revaccinated.						Vaccinated in incubation.		
				Successfully.			Unsuccessfully.			Successfully.			Unsuccessfully.					
	Cases.	Deaths.	Per ct.	Cases.	Deaths.	Per ct.	Cases.	Deaths.	Per ct.	Cases.	Deaths.	Per ct.	Cases.	Deaths.	l'er ct.	Cases.	Deaths.	Per ct.
0– 5 years	39	28	71.7	4	1	25.0	5	3	60.0	0	0	0	0	0	0	13	6	46.1
6–10 "	1	0	0	10	2	20.0	3	1	33.3	1	0	0	1	1	100	0	0	0
11–20 "	4	2	50.0	68	7	10.2	3	1	33.3	8	1	12.5	14	0	0	4	1	25.0
21–30 "	19	13	68.4	257	45	17.8	3	2	66.6	45	3	8.5	37	4	10.8	11	0	0
31–50 "	12	7	58.3	287	75	26.1	2	1	50.0	35	7	20.0	44	8	18.1	10	0	0
Above 50 "	2	2	100	54	29	39.1	2	0	0	10	3	30.0	3	1	33.3	1	1	100

[1] Report on 1000 cases of smallpox in Westham-Union Hospital. Lancet, July 22, 1882.

[2] Delom. De l'influence de la vaccine sur la variole. Thèse de Paris, 1901.

Although vaccination is not compulsory in France, most of the inhabitants of that country have undergone at least one inoculation. A certificate of vaccination is required of children to be admitted to schools. All recruited men to the regiments are revaccinated. The influence of the vaccinations practised in the army explains why men from twenty to thirty years of age are far less frequently attacked by variola than women. In large administrations revaccinations are often practised. According to information, however, which the author obtained during the last epidemic, private establishments are often better organized from this standpoint than public establishments. Furthermore, a measure has been adopted which seems to have very gratifying results: When a case of variola is reported in a house a vaccine-bearing heifer is sent to the house and employed for vaccinating all the residents free of charge. Many persons who would not otherwise take the trouble thus consent to be inoculated at home. Owing to these various measures variola has been considerably decreased; the epidemic, however, which recently prevailed shows that it may easily again be increased. It would, therefore, be advisable to do in France what is being carried out in a great number of countries, notably in Germany. Two inoculations suffice, on condition, of course, that all the inhabitants be submitted to it. One to be practised during first childhood (under two years of age), the other at the age of twenty years. The efficacy of the method is demonstrated by German statistics. The results are so clear that some authors have declared variola to be a disease of historical interest, since it is no longer observed in civilized countries.

Immunization by Attenuated Viruses. Instead of introducing into the organism a mild natural virus capable of conferring immunity, modified infectious agents may be employed, namely, such agents as have been deprived of part of their virulence, in other words, attenuated viruses. Such is the principle of a new method called Pasteurian vaccinations.

Attenuation may be obtained by a great number of procedures. Most of these consist in cultivating the virulent agent under dysgenesic conditions or disturbing its vitality by physical or chemical means. The age of cultures, heating, exposure to sun rays, development at high temperatures, the addition of antiseptic substances to the culture medium, the influence of compressed oxygen—such are the most usual procedures. Let us add to these inoculation into certain animals: the virus becomes exalted for the species upon which

the experiment is performed, while it becomes attenuated as regards another species, a result which may be employed as an argument of the original unity of variola and of vaccinia. However this may be, Pasteurian vaccinations are exclusively employed in veterinary medicine and give remarkable results against anthrax. By means of various systems of vaccination against anthrax animals sensitive to this disease have successfully been rendered refractory. Everyone remembers the famous experiment of Pouilly-le-Fort, where Pasteur conclusively demonstrated the value of his method. At present there is not the slightest shadow of doubt as to the efficacy of the method. From 1882 to 1894, 1,788,677 sheep have been vaccinated in France, and their mortality has been 0.94 per cent., while formerly it reached 10 per cent. As regards cattle, 200,962 have been inoculated, and the mortality has fallen from 5 per cent. to 0.34 per cent.[1] Numerous laboratories of vaccination have been organized in foreign countries (Vienna, Madrid, Turin, Buenos Ayres, Odessa, etc.), and their results have confirmed the efficacy of the method.

Vaccination against Hydrophobia. These results suggest the question whether vaccines could not act even after the introduction of an active virus. It was likewise Pasteur who took up and solved this problem. Into individuals bitten by a rabid animal are practised injections with the diseased spinal cord attenuated by desiccation. A refractory state is thus created which develops more speedily than the disease. Immunity is immediately manifest to prevent the propagation of the active virus and enable the organism to destroy it.

It was by studying the action of the hydrophobic virus and by seeking to vaccinate against it that Pasteur was led to this new result. It should not be forgotten, however, that the first attempt of vaccination against hydrophobia is due to Gautier. In a note presented to the Institute, January 25, 1881, this scientist announced that the injection of hydrophobic saliva into the veins of sheep does not produce hydrophobia, but confers immunity. This result, which was confirmed August 1, 1881, in a contribution in which the author announced that he had vaccinated nine sheep and one goat, was of considerable interest. Unfortunately, the method was unfit for practical purposes, because the introduction of saliva is an unreliable and dangerous method. Intravenous injection, which succeeds so well

[1] Chamberland. Résultats pratiques des vaccinations contre le charbon. Annales de l'Institut Pasteur, 1894.

with ruminants, in most cases causes death when it is applied to other animals, and particularly to the dog.

In 1881 Pasteur, Chamberland and Roux, and Thuillier published a method which did away with all the uncertainty of inoculation of saliva: This was the employment of the hydrophobic spinal cord, an emulsion of which was injected beneath the dura mater. In 1882 Pasteur and his collaborators announced that of three dogs inoculated two perished and one survived after having been sick this animal had become refractory; it was subsequently twice inoculated by trepanation, but did not become hydrophobic. From that time on Pasteur saw several dogs inoculated with virulent matter resist the experiment and become refractory. He even noticed that large doses of hydrophobic virus, when injected beneath the skin, produce hydrophobia less frequently and immunity oftener than medium doses. This result, highly interesting from the standpoint of pathological physiology, was confirmed by various experimenters, notably by Bardach. Under these conditions, however, vaccination appears as an exceptional fact; it was, therefore, necessary to prepare a virus incapable of killing the dog, but sufficient to increase its resistance and render it refractory to more and more energetic agents. This attenuation of virulence Pasteur obtained by transferring hydrophobia from the dog to the monkey. As passages are practised upon the latter animal the activity of the virus weakens, a fact proved by the progressive lengthening of the period of incubation. If the virus is then transferred to the rabbit, it becomes exalted; the period of incubation gradually decreases until the minimum point is reached.

This minimum delay of incubation, obtained at about the hundredth passage, is invariable, and amounts to six or seven days. The virus is then said to be "*fixed.*"

Thus, starting from the monkey and passing through the rabbit, one may prepare a series of viruses with progressively decreasing activity. If we inoculate beneath the skin of a dog the more and more virulent spinal cord of a rabbit, beginning with the least energetic, we produce no accident, but confer on the dog immunity against the most virulent virus introduced by trepanation. This result, based upon twenty-three experiments, was announced to the Institute on May 19, 1884, and confirmed by the researches pursued upon forty-two inoculated and forty-two controlled animals, before a commission composed of Beclard, Bouley, Bert, Vulpian, and Vil-

lemin. When bitten by rabid dogs, not one of the vaccinated animals succumbed, while most of the controls perished.

The discovery was, therefore achieved, but the method was not practical. It was necessary to suppress the passage through the monkey and attenuate the virus without employing this animal. This new problem was likewise solved by Pasteur and his collaborators. They took rabbits which had died from the "fixed" virus, and they found that their spinal cords lost much of their virulence under the influence of desiccation. In order to obtain this result, these spinal cords are detached with the greatest aseptic precautions; they are suspended in a vial closed with cotton and at the bottom of which there are fragments of potassium. From the thirteenth to the fourteenth day on, the cord is found to have lost its virulence; the shorter the period of desiccation the greater is the activity of the cord. In 1885 Pasteur announced that, by means of spinal cords thus prepared, he had rendered fifty dogs refractory to inoculations practised into the skin and even beneath the dura mater.

In view of the results given by this memorable experiment, an attempt might be made to apply to man the new method. The occasion soon presented itself. As is well remembered, the first attempt was made upon young Joseph Meister, bitten July 4, 1885. After consulting Professors Vulpian and Grancher, Pasteur practised his mode of treatment upon this child, who seemed to be condemned to certain death by the number and depth of the bites. The result exceeded all expectation. The patient recovered, and sixteen years after the inoculation, he was in perfect health.

After this first case, which was reported in October, 1885, very large numbers of individuals have come to the laboratories of Pasteur from all parts of the world. More than ten thousand have been treated in Paris; at least as many have been similarly treated in the Pasteur Institutes of foreign countries. Pasteur first employed a simple method, which consisted in injecting beneath the skin the spinal marrow of the fourteenth day, then successively those of the thirteenth, twelfth, until the fifth day. Each specimen of marrow was injected once; the treatment, therefore, lasted ten days. This method was not sufficient for grave cases; hence, Pasteur abandoned it and adopted the so-called intensive method, which consists in repeating the inoculations, in making the vaccinations at shorter intervals, and in administering more virulent marrow. The treatment is modified according to the gravity and especially the seat of

the bites. The method is carried out as follows: A fragment of spinal marrow about 3 mm. long is taken and triturated in 1 c.cm. of bouillon and injected beneath the skin in the hypochondriac region. The injection is somewhat painful, but gives rise to no disturbance except in the last two days, when the puncture becomes the seat of a small erythematous and itching patch. First, a specimen of the marrow of fourteen or thirteen days is employed, then progressively the marrows of twelve and eleven until that of the third day is reached, the virulence of the latter being about the same as that of the fresh marrow. The quantity injected may reach 3 c.cm. in the case of marrows of little activity—those of the fourteenth to seventh day—no more than 2 c.cm. of the marrow of less than seven days are given. In grave cases intervention must be prompt, therefore four injections a day are given. The first day the marrows of the fourteenth and thirteenth days are employed by two punctures, one in each hypochondriac region; in the evening of the same day the marrows of the twelfth and eleventh days are injected. The following day the marrows from the tenth to the seventh day are used. On the third day of the treatment two injections are given with the marrow of the sixth day. After that, one injection is given daily with the more virulent marrows. When the marrow of the third day is reached a new series is begun, starting with the marrow of the fifth day; then recourse is had to a third and even a fourth series. At times, at the end of the treatment the patient complains of pain at the point of the cicatrices; in such cases a new vaccination is undertaken according to the intensive method, and the symptoms often disappear. It is thus conceivable that the vaccination must not be applied in the same manner in all patients; we cannot, however, dwell upon the details of the treatment, which varies with each case, and the duration of which is limited between fifteen and twenty-two days.

Pasteur's method is at present employed in a great number of countries; it has at times undergone more or less important modifications. Thus, in countries where rabbits are smaller than ours the spinal marrows dry rapidly and lose their virulence more speedily. It is, therefore, possible to begin the injections with marrows of the tenth or eighth days, as is done by Babès in Bucharest, and Bujwid in Warsaw. The latter experimenter gives the series of marrows from the twelfth to the third days in four days, and repeats the same series three times. In desperate cases Bardach and Gamaleia have

employed the entire series of viruses each day for three days in succession, reaching the specimen of one day. It is unnecessary to mention all the modifications of the treatment. Reference must be made to the attempt of Ferran, who did not hesitate to inject non-attenuated viruses. Although his method seems to have given good results, it has produced disturbances in Milan at the hands of Bareggi.

It has likewise been possible, at least in the case of animals, to confer immunity against hydrophobia by other procedures. Dr. Galtier's experiments have already been alluded to. More recently Drs. Nocard and Roux have taken up the method of intravenous injections by substituting for saliva a more certain virus furnished by an emulsion of spinal marrow. They have thus succeeded in vaccinating sheep, and even saving several into the eyes of which, twenty-four hours previously, they had inoculated the virus of hydrophobia. Intravenous injection may also confer immunity upon the dog, provided a weak virus be first employed, and then gradually specimens of progressively growing activity (Protopopoff). Moreover, vaccinations have also been practised by means of diluted viruses (Bardach), as well as with viruses attenuated by heat (Babès).

The brief history of facts above given demonstrates that the virus of hydrophobia, when rendered inoffensive by one of the foregoing procedures, may confer immunity. The mechanism by which this effect is obtained has been a question. In view of the results observed in other infectious diseases, an effort has been made to learn whether antirabic vaccination does not depend upon soluble substances elaborated by the agent of hydrophobia. Prof. Bouchard attempted to vaccinate by means of marrow triturated in water and filtered through porcelain. The fluid thus obtained did not confer immunity against inoculation later practised beneath the dura mater. This negative result was confirmed by De Blasi and Travali. These authors succeeded, however, in rendering animals refractory to intravenous inoculations by the same procedure. Babès and Lepp have likewise conferred immunity by injecting cerebral substance sterilized by heating at 176° F. (80° C.).

Pasteur thought that his procedure did not attenuate the virus but decreased its quantity. A rabbit into which this so-called attenuated virus is injected succumbs in thirty days, and its medulla as well as the fixed virus, when inoculated into a second rabbit, kills the latter in seven days. Desiccation is supposed to destroy the virus more rapidly than the vaccine, so that the marrows rapidly lose

their noxious properties, while they preserve their vaccinating properties for a longer time.

The attenuation of marrow attributed by Protopopoff and Blasi and Russo-Travali to the action of heat seems to depend upon a phenomenon of oxidation brought about by heat. Thus, Zagari has found that marrows placed in dry air remain virulent for ten days at a temperature of 68° F. (20° C.), and for only sixty-six hours at 95° F. (35° C.). The virulence is more rapidly lost in hydrogen; it is preserved longer *in vacuo*, and especially in carbonic acid. If it disappears under these conditions, it is due to the fact that the marrow, at the time it is taken from the body, retains a certain amount of oxygen which serves the ulterior phenomena of oxidation. The immunity conferred by the Pasteurian method seems to be fairly durable. It persists for two years in dogs. It may be transmitted even by heredity: at least this is what seems to be proved by a very interesting fact published by Högyes: of four young born from a refractory couple and inoculated in the eye when three months old, one died; two succumbed after a very long incubation; the fourth survived and resisted two additional inoculations.

Such are the facts that may be recorded in favor of Pasteur's method. They demonstrate the possibility of attenuating or rather modifying the virus of hydrophobia and that this modified virus renders animals refractory to hydrophobia and enables bitten individuals to resist the infection.

Immunization against Cholera, Bubonic Plague, and Typhoid Fever. Haffkin indicated two procedures for vaccinating against cholera. The first consists in injecting an attenuated virus, and eight days later a strong virus. The second procedure is based upon the employment of cultures sterilized by a 0.5 per cent. solution of carbolic acid. Since 1893 the anticholeric vaccine has been inoculated in India into more than 100,000 individuals. The mortality is said to have been diminished by about 15 to 20 per cent. However, strange to relate, while cholera is less frequent among vaccinated individuals, it seems to be just as grave when it attacks them.

In order to prevent bubonic plague Haffkin employed cultures of the bubonic bacillus heated to 161.5° F. (72° C.). The immunity thus conferred lasts more than six months. Statistics seem to show that the prophylactic results are quite clear. Morbidity is decreased, and the mortality, which is 62 per cent. in non-vaccinated subjects, falls to 27 per cent.

Finally, let us mention the attempts of Wright, who vaccinates against typhoid fever by means of cultures sterilized by heat. These inoculations have been practised in the army of India, and have reduced the number of cases.

Dangers of Vaccinations. A grave objection may be made against all these methods. An infection, whatever it may be, and however benign that it may be supposed to be, gives rise to a series of disturbances and lesions. It produces in the organism nutritional modifications and changes in the constitution of the fluids, which account for the immunity acquired. The morbid work may be so slight as to be unnoticeable. We cannot, however deny the reality, and consequently we must, in a certain measure, fear these new methods.

Breeders assert that sheep immunized against anthrax do not develop as well as others. Hence, vaccination is practised less regularly in Beauce. The losses caused by a few cases of anthrax are less considerable than depreciation resulting from immunization. Upon the author's advice, Dr. Kaplan[1] studied this question. He examined two lots of sheep, one vaccinated, the other not vaccinated. By watching the animals and weighing them regularly, he found no notable differences. It has also been questioned whether vaccinations could not induce a fatal infection in a predisposed individual who is already sick and suffering. What we have learned from experimentation on microbic associations gives a certain importance to this criticism. This objection has been raised particularly with regard to antirabic treatment. Leaving aside contestable reports, it must be remembered that eminent bacteriologists, like Babès, have cited cases in which vaccinal hydrophobia has given rise to disorders. These cases are undoubtedly exceptional; they do not impair the value of the method, and must not prevent its employment against bites. They must only render us more circumspect when the question is one of prophylaxis.

Serum Prophylaxis. In the presence of the inconveniences resulting from the introduction into the organism of even attenuated living viruses or of toxins, attempts have been made to secure prophylaxis by means of serums. Preventive inoculations have been practised against streptococcic infections, notably puerperal fever; against bubonic plague, tetanus, and diphtheria. Heubner established that injections of antidiphtheritic serum repeated every three weeks com-

[1] Kaplan. Contribution à l'étude du charbon. Son état actuel en Beauce. Thèse de Paris, 1900.

pletely suppressed the contagion in the hospitals. For his part, the author believes that it is better to struggle against contagion by isolating suspicious cases. The author never resorts to preventive injections, and for the last six years has never observed a single internal case. He believes, however, that this method must be employed when several cases occur in an establishment or a family. In other words, preventive serumtherapy must be a method of exception which may render immense service in certain instances, but which must not be laid down as a general rule. There will always be time enough for practising injections of serum when the infection is contracted. In order that intervention may be timely, it is necessary to watch with particular care individuals who have been in contact with diphtheria cases. This reservation is confirmed by the fact that physicians who treat diphtheria cases are not in the habit of practising preventive inoculations upon themselves or their families. The same rules are applicable to other serums. If an epidemic of puerperal fever should reign in a ward, it would be advisable to practise prophylactic injections of serum, but we do not advise to thus inject every puerperal woman. Likewise, antitetanic serum should not be employed every time an individual happens to have an abrasion; but it will be useful in certain regions where tetanus is endemic. Lastly, the antibubonic serum, although less efficacious than Haffkin's vaccine, has the advantage of being less dangerous. It may, therefore, be employed at the time of an epidemic.

Thanks to the multiple procedures which we possess at present, it is possible to confer immunity against a great number of infections. A more and more accurate knowledge of pathogenic agents, of their distribution in nature, their mode of penetration into the organism has led to various hygienic measures which have lowered both morbidity and mortality. The isolation of contagious cases, sterilization of contaminated objects, the destruction of germ-bearing organic particles often suffice to arrest the spread of disease. These divers methods are no more than a systematization of ancient ideas. Antiquity had a certain foresight of the results obtainable by prophylaxis, as is indicated by the hygienic laws of Moses and, in the middle ages, the creation of lazarettos and quarantines. What belongs to the modern epoch is the formulation of precise rules based upon experimental facts—substitution of scientific data for intuition.

Alongside of other hygienic measures there arises a new method of prophylaxis, viz., vaccination, likewise an ancient method originated

in China. It was not until about the middle of the eighteenth century that variolization was introduced into Europe. It was not long employed. A sure and inoffensive method for this uncertain and dangerous procedure was substituted by the genius of Jenner. A century later another genius, Pasteur, demonstrated that an artificially modified virus could be placed by the side of a naturally inoffensive virus. A new prophylactic method thus took its position among the means which enabled mankind to fight infections. Finally, the third method is that which was developed about ten years ago as a result of Behring's and Kitasato's labors.

Prophylaxis by hygiene—*i. e.*, by isolation and disinfection—prophylaxis by Jennerian vaccination, by Pasteurian vaccination, by serumtherapy—these are the great methods which science at the beginning of the twentieth century places at the disposal of mankind for combating epidemics, arresting their march, and lowering their mortality.

INDEX.

ABSCESS of liver, 220
produced by serum injections, 739
Actinomyces, biologic characters of, 314
cultivation of, 315
Actinomycosis, 314
etiology of, 317
evolution of, 317
inoculations of, 316
Adenopathies in smallpox, 386
syphilitic and tubercular, 386
tracheobronchial, 467
Age, influence of, upon prognosis, 632
Albuminuria caused by serum injections, 742
Alimentary canal. See also Digestive apparatus.
antisepsis of, 668, 672
combined infections in, 148
gangrene of, 241
infection by, 105
putrefactions in, 114
suppurations of, 214
Alimentation, 841
Aliments. See also Fasting.
rôle of, in the transmission of infections, 75
Ameba, varieties of, 41
Amyloid degeneration, 328
Anginas, treatment of, 662
Anthrax, intraplacental transmission of, 581
symptomatic, toxin of, 126
toxin of, 126
Antipyrin, action of, on hectic fever of tuberculosis, 802
use of, at terminal period of infection, 803
Antisepsis of alimentary canal, 668
by chemical agents, 653
general, 673
of genital and urinary organs, 661
of intestine, 672
of mouth, 662
by physical agents, 652
of respiratory passages, 665
of serous membranes, 671
of skin, 659
Antiseptics, 657
Antithermics, chemical, 801
Antitoxinic method, 675
Aphasia, 409
Apparatus, circulatory. See also Heart and Arteries.
influence of infections upon, 443
treatment of cardiovascular manifestations, 825
Appendicitis, experimental, 215
Arteries, action of infections upon, 453
Arteriosclerosis, rôle of infections in development of, 455
Arthropathies, infectious, 440
produced by serum injections, 741
Aspergillus eurotium repens, 40
flavescens, 40
fumigatus, 40
nidulans, 40
nigricans, 40
Astringents, 791
Autobacteremia, 247
Autoinfections, 78, 92
Autointoxications, 78

BACILLI, 37
classification of, 38
Bacillus, colon, toxins of, 128
of glanders, biology of, 374
septicus putidus, toxins of, 127
of tuberculosis, biology of, 277
Bacteria accidentally pyogenic, 190
action of chemical agents on, 55
of heat on, 53
of light on, 54
of organic fluids on, 553
of pressure on, 50
of serum on morphology of, 557
anaërobic pyogenic, 189
classification of, 37
curved, 37
determination of, 43
distribution of, within normal organism, 79
general characters of, 43
importance of number of, in the development of infections, 98
influence of various external agents upon, 50
mode of action of, 108
modes of entrance of, 101
non-specific, classification of, 38
parasitic, 35
passage of, from a saprophytic to a pathogenic life, 36
pathogenic, 35

Bacteria, polymorphism of, 43
pyogenic, 185
relation of, to algæ, 35
rôle of, in development of infections, 98
saprophytic, 35
search for pathogenic, by microscopic examination and cultivation, 607
selective injuriousness of, 100
specific, classification of, 39
pyogenic, 190
toxins of, 120
variability of functions of, 46
of pathogenic properties of, 49
variations in virulence of, 99
Bacterial ferments, 47
pigments, variability of, 47
Bacteriology, determinism in, 61
of gaseous gangrene, 232
of septicemia, 248, 258
Bacteriotherapy, 681
Balneotherapy. See Baths.
Baths, cold, 793
lukewarm, 793
Bicarbonate of soda, influence of, on protective action of liver, 161
Blood, action of venous, upon temperature, 350
bacterioscopic examination of, 367
microscopic study of, 363
modifications in, caused by serum injections, 745
of, in course of infections, 359
protective rôle of, 761
rôle of, in thermal regulations, 348
toxicity of, in some infections, 132
Blood-letting, 805
Bone-marrow, in infections, 369
lesions of, in infections, 376
modifications of, in experimental infections, 370
normal anatomy and physiology of, 369
reactions of, in man, 373
semeiology of, 377
Bones, infections in, 440
Bronchi, 457
Bronchitis, 457
varieties of, 457
Bubonic plague, immunity against, 860
serumtherapy of, 707
Buccopharyngeal manifestations in scarlatina, 471
in smallpox, 472
suppuration, 213
Bulbar manifestations, 411

CALCIUM chloride. See Chloride of calcium.
Calomel, 771
Cancer, inoculations of, 321
Cardiovascular manifestations, treatment of, 825
Caustics, 790
Cells, degenerations of, 324–332
Cephalalgia, 405
in infections, 405
Cerebral manifestations in infections, 404
Chloride of calcium, 787
Cholera, crisis in, 526
immunity against, 860
serumtherapy of, 700
toxin of, 125
Choleriform enteritis, 477
Chorea, 425
crisis in, 526
serumtherapy of, 700
Cinchona, 677
Circulatory apparatus. See also Heart and Arteries.
influence of infections on, 443
treatment of cardiovascular manifestations, 825
disorders, rôle of, in gangrene, 230
Clothing, rôle of, in transmission of infections, 74
Cocci, 37
Colon bacillosis, 188
serumtherapy of, 702
toxins of, 128
Coma, 408
Contagion, definition of, 18
Convalescence, 527
hygiene of, 844
Convulsions, 410
Crises in cholera, 526
in chorea, 526
definition of, 518
in erysipelas, 524
in pneumonia, 521
in scarlatina, 525
in typhus, 524
in various infections, 525
Cultivation, search for pathogenic agents by, 607
Cytologic examination, 617

DEATH, 535
Declaration of contagious diseases, 845
Degeneration or degenerations, amyloid, 328
causes of, 326
cellular, 324–332
fatty, 327
pigmentary, 331
varieties of, 324–326
Delirium, 406
Determinism in bacteriology, 61
Diagnosis according to chemical modifications in fluids, 623
of infectious diseases, 606–631
inoculation from the point of view of, 613
by microbic toxins, 624
rules of clinical, 627
by therapeutics, 624

Diagnosis, vesicatory test in, 618
Digestive apparatus. See also Alimentary canal and Stomach.
infections in, 469
influence of infections on, 469
treatment of disorders of, 831
Diphtheria, serumtherapy of, 703
Diphtheritic paralysis, 420
Diseases, infectious. See Infections.
Dysenteriform enteritis, 477
Dysentery, amebic, 476
bacterial, 476
Dystrophies, of infectious origin, 598

EAR, auricular suppurations, 214
Embolism, 335
Emunctories, protective rôle of, 762
Endocarditis, 449
Endomyces albicans, 303
Enterites, choleriform, 477
dysenteriform, 477
Epidemics, 67
influence of, upon prognosis, 633
variations of, with countries and epochs, 95
Epilepsy, 425
Ergot, 789
Ergotin, 771
Eruption, relationship between intensity of eruption and gravity of disease, 434
Eruptive fevers, serumtherapy of, 730
transmission of, 586
Erysipelas, crisis in, 524
treatment of, by lukewarm baths, 800
Erysipelatous paralysis, 422
Erythemata, mechanism and variability of infectious, 439
Etiological conditions, importance of, in diagnosis, 634
Etiology of infections, 64–97
Examination, cytologic, 617
microscopic, search for pathogenic agents by, 607
Exanthemata, 431
produced by serum injections, 739
Experimentation, rôle of, in study of infectious diseases, 58
Exudates, serous, 174
Eye, ocular suppurations, 214

FAMILY, rôle of, in infections, 86
Farcina bovidæ, 39
Fasting, influence of, upon protective action of liver, 160
Fatigue, influence of, on infections, 94
Fatty degeneration, 327
Febrile manifestations, treatment of, 819
Fecal matters, toxicity of, 116
Ferments, bacterial, 47
Fetid pleurisy, 240
Fever or fevers, 338
caused by injection of serums, 741
Fever, characters of, in some infections, 355
classification of, 339
definition of, 338
eruptive, serumtherapy of, 730
mechanism of, 346
rôle of blood in, 348
semeiological value of, 358
therapeutics of, 792
typhoid, autogenic, 82
clinical forms of, 516
contraindications of cold bathing in, 795
immunity against, 860
serumtherapy of, 729
toxin of, 131
Fluids, organic. See also Blood and Serum.
action of, on bacteria, 553
modifications in, 337
various, employed in therapeutics, 697
Food. See also Aliments.
rôle of, in the transmission of infections, 75
Fungi, infectious, 39

GALLINÆ, tuberculosis of, 290
Gangrene, 225–243
Gangrene, causes favoring development of, 227
definition of, 227
gaseous, bacteriology of, 232
toxin of, 126
various agents of, 233
of limbs, 235
of liver, 241
of lungs, 238
of mammary glands, 235
principal agents of, 232
pulmonary, 238
rôle of chemical agents in, 230
of circulatory disorders in, 230
of intoxications in, 231
of mechanical and physical agents in, 229
of nervous system in, 231
of spleen, 241
treatment of, 781
in various parts of organism, 235
Gangrenous lesions, treatment of, 781
pleurisy, 240
Gastrointestinal putrefactions, 114–120
Generation, spontaneous, 34
Genital organs, antisepsis of, 661
Genito-urinary organs, antisepsis of, 661
gangrene of, 241
infection by, 106
influence of infections on, 490
suppurations of, 221
Germicidal substances, rôle of spleen in production of, 381
Glanders, animals sensitive or refractory to, 275

Glanders, bacillus of, biology of, 374
etiology of, 275
pathological anatomy of, 276
serumtherapy of, 709
toxins of, 131
Glucose, influence of, upon protective action of liver, 160
Guaiacol, 804

HEART. See also Myocarditis, Endocarditis, and Pericarditis.
action of toxins upon, 444
functional disorders of, 443
post-infectious hypertrophy of, 448
Hemiplegia, 409
Hemorrhages, caused by injections of serum, 744
causes of, general, 785
local, 783
therapeutic indications of, 786
treatment of, 783
Hemorrhagic pleurisy, 467
septicemia, 245, 255
Heredity, 580–605
Heterointoxications, 64
of gastrointestinal origin, 118
Humoral modifications of lymphatic origin, 387
Hydrocele, 776
Hydrophobia, serumtherapy of, 735
vaccination against, 855
Hygiene of convalescence, 844
individual, 837
of sick, 840
of sick room, 837
social, 845
Hyperthermia, 338

IMMUNITY, acquired, 559
congenital, 599
individual, 88
mechanism of, 551–579
natural, 557
Immunization against cholera, typhoid fever, and bubonic plague, 860
by attenuated viruses, 854
by means of strong viruses, 847
Incubation, 495
importance of duration of, in prognosis, 635
period of, 22
Infantile paralysis, 417
Infection or infections, abortive, 512
action of, on organs of sense, 428
of poisons upon, 91
of, on respiratory apparatus, 456
autogenic origin of various specific, 81
bones in, 440
cephalalgia in, 405
circulatory apparatus in, 443
classification of, 24
Infection, clinical forms of, 511
combined, 142
in alimentary canal, 148
in respiratory apparatus, 147
of skin, 145
of throat, 145
consequences of, 541–550
cutaneous manifestations in, 429
origin, 102
declaration of, 845
definition of, 24
diagnosis and prognosis of, 606–641
digestive apparatus in, 469
eruptive, 26
etiology of, 64–97
evolution of, 494–540
history of, 30
hygiene and prophylaxis of, 537–863
incubation of, 495
individual immunity from, 88
predisposition to, 88
influence of age on, 88
of autoinfections on, 92
of family on, 86
of fatigue and overwork on, 94
on genital organs, 490
of individuals on, 88
on neuropathies, 427
of poisons on, 91
of seasons on, 84
of sex and age on frequency of, 89
intraplacental transmission of chronic, 593
of human, 583
invasion of, 503
lesions of bone-marrow in, 376
lymphatic glands in, 382
meaning of, 17
miasmatic, 18
modifications of blood in course of, 359
bone-marrow in experimental, 370
muscular system in, 438
nervous system in, 403
neuroses following, 423
non-specific, 29
passage of acute to a chronic condition, 531
pathogenesis of, 98–134
rôle of, in development of arteriosclerosis, 455
of, in development of general paralysis, 408
secondary, 144
simultaneous occurrence of two, 143
specific, 25, 29
spinal cord in, 412
spleen in, 378
stationary period of, 506
suprarenal capsules in, 400
termination of, 516
therapeutics of, 642–836
through alimentary canal, 105

Infection through genito-urinary organs, 106
nervous system, 106
organs of sense, 106
respiratory passages, 103
serous membranes, 106
vascular system, 107
thymus in, 387
thyroid gland in, 393
transmission of, by contact, 65
through aliments, 75
air, 69
clothing, 74
invertebrates, 73
plants, 74
by soil, 72
by water, 71
tumors and, 319
venereal, 27
virulent, 31
with nodular productions, 28
with septicemic tendency, 27
Infectious agents, action of, 24
classification of, 35
mode of entrance of, 101
Inflammatory exudates, treatment of, 772
manifestations, treatment of, 765
Infusoria, 34
Inoculation or inoculations. See also Vaccination.
of actinomyces, 316
of cancer, 321
from a diagnostic standpoint, 613
subcutaneous, 102
of tuberculosis, 288
Insanity in tuberculosis, 407
Intestine, antisepsis of, 672
choleriform and dysenteriform affections of, 477
disturbances and lesions of, in infections, 474
Intoxications, rôle of, in gangrene, 231
Intraplacental transmission of anthrax, 581
of chronic infections, 593
of human infections, 583
Invasion, 503
importance of mode of, in diagnosis, 635
Invertebrates, rôle of, in transmission of infections, 73
Iodine, 678
Ipecac, 790

KIDNEYS, influence of infections on, 489
rôle of, in thermogenesis, 351
treatment of renal disorders, 835

LACTATION, influence of infections on, 491
Larynx in infections, 456
Leprosy, serumtherapy of, 709
Leptothrix, 37
Lesion or lesions, local, evolution of, 508
local, rôle of, in suppurative processes, 198
reparation of traumatic and of toxic infectious, 541–545
suppurating, generalization of, 200
Leucocytes, variations of, 364
Limbs, gangrene of, 235
Liver, abscesses of, 220
action of, on microbic poisons, 162
gangrene of, 241
general characters of infected, 486
influence of bicarbonate of soda on protective action of, 161
of fasting upon protective action of, 160
of glucose upon protective action of, 160
of infectious diseases on, 485
protective rôle of, 156, 159, 758
rôle of, in thermogenesis, 351
semeiology of infectious, 487
Lungs. See also Respiratory apparatus.
classification of lesions of, of infectious origin, 460
gangrene of, 238
in infectious diseases, 458
normal physiology of, 458
protective rôle of, 156, 760
rôle of, in thermogenesis, 351
Lymphatic glands, histological study of, 384
in infections, 382
inflammation of, in variola, 386
protective rôle of, 154

MALLEIN, 625, 694
Mammary glands, gangrene of, 235
Measles, buccopharyngeal manifestations in, 470
Medication, depletive, 771
physiological, 757
specific, 676
symptomatic, 819
vasomotor, 771
Meningitis, infectious, 426
Menstruation, influence of infections on, 490
Mercury, 678
Meteorological influence on infections, 84
Miasmatic diseases, 18
Microbes. See also Bacteria.
association of, 135–153
modifications of action of liver upon, 159
necrosing rôle of pyogenic, 234
passage of, through placenta, 580
toxins of pyogenic, 129
Microbic associations, 135–153, 160
products, favorable to infection, 137

Milk, passage of active substances into, 568
rôle of, in the transmission of infections, 75
Mouth, antisepsis of, 662
buccopharyngeal manifestations in measles, 470
in scarlatina, 471
in varicella, 472
in variola, 472
in various infections, 472
Murmurs, non-organic, of heart, 443
Muscles or muscular system in infections, 438
Mycoses in man, 319
Myelitis, 414
in various infections, 417
Myocarditis, acute, 446

NEPHRITIS caused by serum injections, 742
Nervous connections, 337
manifestations, treatment of, 821
system, connections of, 337
infection through, 106
in infections, 403
rôle of, in development of gangrene, 231
nervous alterations in suppuration, 197
suppuration of, 222
treatment of manifestations of, 821
Neurites, 419
Neuropathies, influence of infections on, 427
Neuroses following infections, 423
post-infectious, 423
Nocardia farcinosa, 39
Nodular infections, 272–322
lesions, treatment of, 783
Nose, nasal suppurations, 213

OBNUBILATION, 408
Oidiomycosis. See also Endomycosis.
biology of parasite of, 302
experimental, 307
histological study of, 309
nature of, 312
Oidium albicans, 302
characters of cultures of, 304
rôle of, in human pathology, 304
Omentum, protective rôle of, 154
Oömyces, 40
Oöspora asteroides, 39
Organism, defenses of, 154, 181
influence of infections on, 359–493
reactions of, against infections, 166
inflammatory, 168
return of, to a former state of its evolution, 549
Organism, suppuration in various parts of, 212
Organs. See also Tissues and Cells.
action of various, upon microbic poisons, 164
contiguity of, 334
modifications of hematopoietic, 368
of sense, action of infections on, 428
infection by, 106
Osteopathies, infectious, 440
Overwork, influence of, upon infections, 94

PANCREAS, action of infections on, 488
suppurations of, 221
Paralysis or paralyses, acute ascending, 414
diphtheritic, 420
erysipelatous, 422
general, rôle of infections in development of, 408
infantile, 417
scarlatinal, 422
Parasites capable of inducing suppuration, 183
pyogenic, animal, 192
relative frequency of, 193
vegetable, 191
Parasitic agents, action of, 23
Parrots, tuberculosis of, 293
Pathogenesis of infections, 98–134
Pathogenic agents, mode of action of, 108
of entrance of, 101
search for by microscopic examination and cultivation, 607
selective injuriousness of, 100
Pericarditis, 452
Peritonitis, tubercular, 775
Peroxide of hydrogen in treatment of gangrene, 781
of hemorrhages, 792
Perspiration, 437
Phycomyces, 40
Pigmentary degeneration, 331
Pigments, bacterial, variability of, 47
Placenta, intraplacental transmission of chronic infections, 593
passage of microbes through, 580
Plants, rôle of, in transmission of infections, 74
Plasmodium malariæ, 42
Pleura, lesions of, in infections, 465
Pleurisy or pleurisies, gangrenous and fetid, 240
hemorrhagic, 467
purulent, 467
serous, 465
treatment of, 772
Pneumococcosis, serumtherapy of, 710
Pneumococcus, 187
toxin of, 130

Pneumonia, clinical forms of, 515
crisis in, 521
Poisons. See also Ptomains and Toxins.
action of, on infections, 91
liver on, 162
of various organs on microbic, 164
defenses of organism against, 162
found in infected organisms, 131
microbic, 109
ptomain, 113
putrid, 109
Predisposition, 88, 551–579
congenital, 599
Pregnancy, influence of infections on, 491
Prognosis, bases of, at stationary period, 635
general rules of, 639
importance of duration of incubation and of mode of invasion in, 635
of infectious diseases, 631
influence of age on, 632
of epidemics on, 633
of sex on, 633
of serumtherapy accidents, 747
Prophylaxis by serum, 861
Proteobacillosis, serumtherapy of, 712
Protozoa, infectious, 41
Pseudomembranes, 176
diphtheritic, 177
Pseudomembranous exudates, treatment of, 781
Pseudotuberculosis, 295
by animal parasites, bacterial, 298
human, 301
micotic, 297
by inanimate substances, 295
Ptomains. See also Poisons and Toxins.
table of, 113
Pulmonary gangrene, 238
Purulent exudates, treatment of, 777
foci, development and evolution of, 208
pleurisy, 467
Pus. See also Suppuration and Purulent Foci.
physical and chemical characters of, 204
Putrefactions, gastrointestinal, 114–120
Pyemia. See also Septicemia.
of animals, 255
attenuated form of, 264
clinical evolutions of, 261
distinction of, from septicemia, 244
experimental, 250
history of, 251
human, 257
relationship between variola and, 265
relative frequency of agents of, 260
of saprophytic origin, 254
Pyocyanobacillosis, serumtherapy of, 712
Pyramidon, 803

QUININE, 677

RABBITS, epizootic purulent rhinitis of, 256
experimental variola of, 268
Rabel's water, 786
Rabies. See Hydrophobia.
Race, rôle of, in infections, 86
Reactions, general, 333-358
Recurrences, 530
Relapses, 529
Renal disorders, treatment of, 835
Respiratory apparatus. See also Lungs.
action of infections on, 456
antisepsis of, 665
combined infections in, 147
disorders of, 460
remote consequences of infective lesions of, 468
suppuration of, 214
manifestations in, 827
passages, antisepsis of, 665
infections through, 103
Rhatania, 791

SALICYLIC acid, 680
Scarlatina, buccopharyngeal manifestations in, 471
crisis in, 525
Scarlatinal paralysis, 422
Season, influence of, in infections, 84
Secretions, passage of active substances into, 568
sudoral, 437
Septicemias of animals, 255
attenuated forms of, 264
bacteriology of, 248
classification of, 246
clinical evolution of, 261
definition of, 244
experimental, 250
hemorrhagic, 245, 255
history of, 251
human, 257
bacteriology of, 258
of intestinal origin, 254
of nasal origin, 253
principal agents of spontaneous, 249
relationship between variola and, 265
relative frequency of agents of, 260
of salivary origin, 253
of saprophytic origin, 254
secondary, 149
localizations of, 151
Serous exudates, treatment of, 772
membranes. See also Omentum.
antisepsis of, 671
infection through, 106
suppurations of, 222
pleurisy, 465

Serum or serums. See also Serumtherapy.
accidents ascribable to injections of, 739, 746
action of, on morphology of microbes, 557, 560
of, on virulence, 557
agglutinating power of, 561
antitoxic properties of, 564
artificial, injections of, 808
indications for, 814
attenuating power of, 562
mode of action of therapeutic, 751
modification of, in acute diseases, 574
of, in animals predisposed to infections, 572
nature and origin of various active substances contained in, 577
prophylactic injections of, 737
prophylaxis, 861
Serumtherapy, 694
accidents ascribable to, 739
of bubonic plague, 709
causes and mechanism of accidents of, 749
of cholera, 700
of chorea, 700
of colon bacillosis, 702
of diphtheria, 703
of eruptive fevers, 730
of glanders, 709
of hydrophobia, 735
of infections whose agents are not well known, 730
of leprosy, 709
mode of action of, 751
of pneumococcosis, 710
of proteobacillosis, 712
of pyocyanobacillosis, 712
of smallpox, 733
of staphylococcosis, 713
of streptococcosis, 714
of syphilis, 736
of tetanus, 722
of tuberculosis, 724
of typhoid fever, 729
of vaccinia and variola, 133
various applications of, 700
Sex, influence of, upon prognosis, 633
rôle of, in infectious diseases, 88
Silkworm disease, 34
Skin, antisepsis of, 659
combined infections of, 145
consequences of cutaneous infections, 436
cutaneous manifestations in infections, 429
suppurations, 213
Smallpox, adenopathies in, 386
buccopharyngeal manifestations in, 472
congenital, 586
cultivation of microbe of, 269
epidemiology of, 67
Smallpox, microbiology of, 267
relation of, to septicemia and pyemia, 265
serumtherapy of, 733
Specific medication or treatment, 676
Spinal cord in infections, 412
Spleen, gangrene of, 241
in infectious diseases, 378
rôle of, in production of germicidal substances, 381
Sporozoa, 41
Staphylococcosis, serumtherapy of, 713
Staphylococcus, 185
Stationary period, 506
bases of prognosis at, 635
Sterilization of morbid products, 839
Stomach, action of infections on, 473
Stomatitis, treatment of, 662
Streptococcosis, serumtherapy of, 714
Streptococcus, 186
Streptothrix, pathogenic, 318
Suckling by infected women, 492
Sudoral secretions, 437
Suette picarde, 96
Suppuration, 182–224. See also Pus and Purulent Foci.
auxiliary causes of, 195
buccopharyngeal, 213
cold, 212
of nervous system, 222
non-microbic, 201
in clinical observations, 203
parasites of, 184
of respiratory apparatus, 214
rôle of general state in suppurative processes, 199
of microbic products in, 203
in various parts of organism, 212
Suprarenal capsule, infections in, 400
Sweat, 437
Sympathies, morbid, 333
Symptomatic anthrax, toxin of, 126
Synergies, functional, 333
Syphilis, adenopathies in, 386
serumtherapy of, 736

TANNIN, 791
Tartar emetic, 771
Temperature, action of microbic toxins on, 341
daily course of rectal, under normal conditions, 356
semeiological value of course of, 358
Termination of infections, 516
Tetanus, serumtherapy of, 722
toxin of, 124
Tetany, 425
Tetracoccus buccalis, 44
Therapeutics, antiseptic method of, 652
antitoxinic method of, 675
bacteriotherapic method of, 681
diagnosis by, 624
of fever, 792
general rules of, in infections, 648

Therapeutics of infectious diseases, 642–836
physiological, 758
serumtherapic method of, 694
specific medication in, 676
various organic fluids employed in, 697
Thermogenesis, rôle of kidneys in, 351
of liver in, 351
of lungs in, 351
Thoracentesis, 772
rules of, 773
Throat, combined infections of, 145
Thymus, histological modifications of, in infections, 390
in infections, 387
primary infection of, 393
Thyroid glands, experimental tumors of, 320
general characters of, in acute infections, 396
in infectious diseases, 393
mechanism and significance of lesions of, 398
normal histology of, 394
Tissues. See also Organs.
germicidal properties of, 569
Toxicity of fecal matters, 116
Toxins, action of microbic, upon temperature, 341
of, upon organism, 122
of tubercular, 287
of cholera, 125
description of principal, 123
diagnosis by microbic, 624
of gaseous gangrene, 126
of glanders, 131
modes of elimination of, 164
of pathogenic microbes, 120
of symptomatic anthrax, 126
of tetanus, 124
of tuberculosis, actions of, 287
of typhoid fever, 131
Trachea, 457
Tracheobronchial adenopathies, 467
Transmission of eruptive fevers, 586
intraplacental, of anthrax, 581
of tuberculosis by contact, 68
by inhalation, 70
Treatment. See also Medication and Therapeutics.
of anginas, 662
antiseptic, of stomatites and anginas, 662
of cardiovascular manifestations, 825
by cold applications, 790
by depletion, 768
of digestive disorders, 831
of disorders of digestive apparatus, 831
of erysipelas, 800
of febrile manifestations, 819
of gangrene, 781
peroxide of hydrogen in, 781
Treatment of hemorrhages, 783
peroxide of hydrogen in, 792
by hot applications, 765
by immobilization, 767
of inflammatory exudates, 772
manifestations, 765
by injections of artificial serum, 808
local, 765
of nervous manifestations, 821
of nodular lesions, 783
of pleurisy, 772
of pseudomembranous exudates, 78
of purulent exudates, 777
by refrigeration, 766
of renal disorders, 835
of respiratory manifestations, 827
by revulsion, 768
of serous exudates, 772
of stomatitis, 662
by thoracentesis, 773
by venesection, 805
Trichinosis, 42
Tubercle, evolution of, 286
histogenesis of, 283
histological study of oidian, 309
Tubercular adenopathies, 386
insanity, 407
peritonitis, 775
Tuberculin, 688
Tuberculosis. See also Tubercle.
of animals, 289
bacillus of, biology of, 277
etiology of, 279
of gallinæ, 290
inoculability of, 288
insanity in, 407
pathological anatomy of, 280
pseudo-, 295
of psittaci, 293
serumtherapy of, 724
toxins of, action of, 287
transmission of, by contact, 68
by inhalation, 70
vesicatory test in diagnosis of, 621
Tumors and infections, 319
experimental, of thyroid gland, 320
Typhoid fever, autogenic, 82
clinical forms of, 516
contraindications of cold bathing in, 795
immunity against, 860
serumtherapy of, 729
toxin of, 131
Typhus, crisis in, 524

URINARY organs, antisepsis of, 661
Urine, modifications of, produced by serum injections, 742
toxicity of, in some infections, 132

VACCINIA, serumtherapy of, 733
Vaccination against hydrophobia, 855
the oidium, 309
of animals, 696
antivariolar, 849
dangers of, 861
prophylactic, 846
Varicella, buccopharyngeal manifestations in, 472
Variola. See Smallpox.
buccopharyngeal manifestations in, 472
relationship between pyemia and, 265
septicemia and, 265
Variola, serumtherapy of, 733
Vascular connections, 335
system, infections through, 107
Venesection, 805
Vesicatory test, 618
Virulence, action of serum upon, 557
variations of, 99
Visceropathies, post-infectious, 545
rôle of previous, in prognosis, 638

YEASTS, pathogenic rôle of, 313

ZYGOMYCES, 40

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